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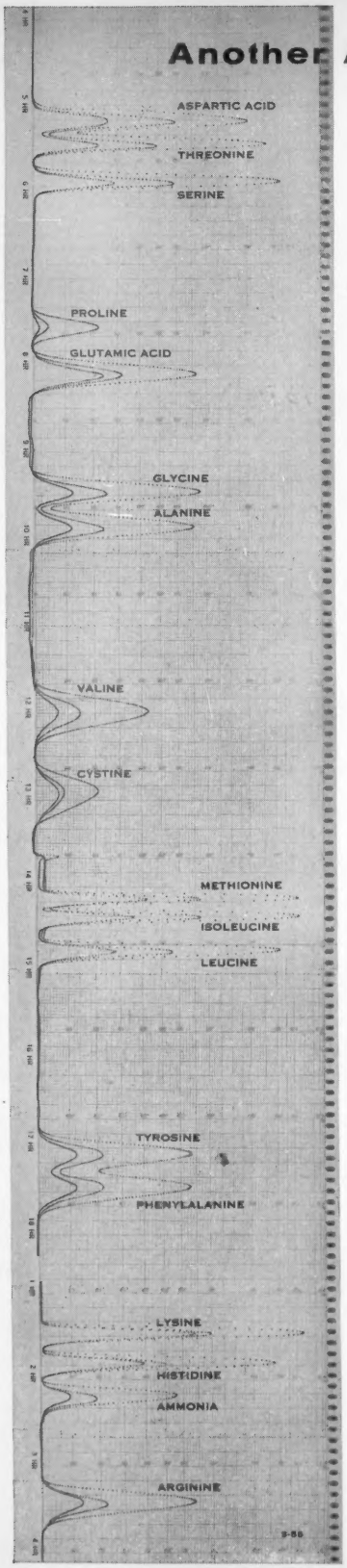

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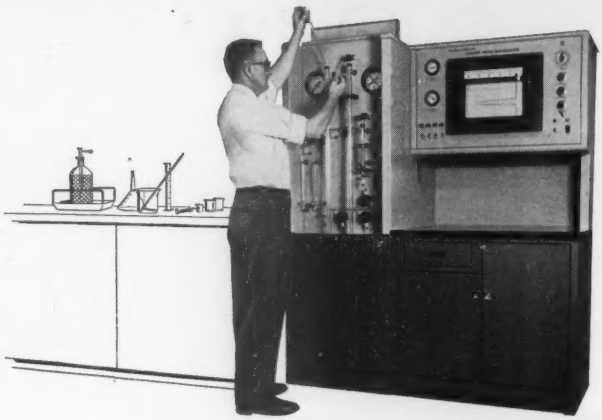

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Reference: *D. H. Spackman, W. H. Stein, and S. Moore, "Automatic Recording Apparatus for use in the Chromatography of Amino Acids", Anal. Chem., 30, 1190-1206, 1958.*

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Psychic Income

One characteristic feature of modern management is its concern about the conditions responsible for good employee morale and job satisfaction. Management has come to realize that pay, although of great importance, is only one among many factors to be considered in employee relations. Some of the other factors important in both job satisfaction and productivity are, according to a committee of the United Nations, "the need to give the staff a sense of belonging to their organization; the opportunity to do constructive work on important problems; adequate recognition of work well done; a reasonable sense of security." These nonfinancial factors constitute "psychic income and are in many cases far more important to the recruitment and retention of superior staff members than pay and fringe benefits" [James M. Mitchell, *Public Personnel Rev.* **17**, 268 (Oct. 1956)].

That employees themselves regard "psychic income" as important is apparent from the results of a study of 17,439 Government and 3317 industrial scientists and engineers [*Attitudes of Scientists and Engineers in Government and Industry* (Government Printing Office, Washington, D.C., 1957)]. Government respondents on the average ranked the following factors in research employment either as of considerable or of great importance on this descending scale: interest potential of the work, integrity of management, opportunity to discover and do creative work, opportunity to move up in the organization, caliber of supervision, living conditions, pay, chance to contribute to basic scientific knowledge, and so on.

One large-scale program designed to stimulate endeavor in Government work was only lightly touched upon in this study. This is the program that began following passage of the Incentive Awards Act of 1954 and that has since been expanding rapidly. The act permits departments to make awards—either cash or honorary—for useful suggestions or superior performance. The number of awards made for suggestions adopted was 35,246 in fiscal 1955, 79,295 in 1956, and 86,209 in 1957; the total cash awarded during the three years amounted to $6.1 million and resulted in estimated savings in Government operations of $176.1 million. Similarly, the number of awards for superior performance was 3856 in 1955, 23,054 in 1956, and 41,340 in 1957 and resulted in estimated savings of $136.1 million.

From an administrative standpoint the program is clearly a success even though the estimate of savings—about $18 for each dollar of awards—may be somewhat inflated. Whether the program stimulates scientific creativity (as opposed to money-saving suggestions) is uncertain, as is its effect on morale and job satisfaction. In those agencies such as the Bureau of Standards and the Office of Naval Research where awards are frequent and in general regarded as based on merit, the employee reaction is favorable; in other agencies where awards are infrequent or where there is dissatisfaction with the mode of selection, the employee reaction is less favorable.

Further experience and study will doubtless show how best to use the awards and indeed whether the program has any effect upon the creativity and job satisfaction of scientists and engineers. Most Government scientists (69 percent) would, if selected for an award, prefer a cash to an honorary award. This is hardly surprising since the cash award constitutes both psychic and real income.—G.DuS.

26 September 1958, Volume 128, Number 3326 SCIENCE

Critique of the Linear Theory of Carcinogenesis

Present data on human leukemogenesis by radiation indicate that a nonlinear relation is more probable.

Austin M. Brues

A question which has interested investigators of cancer for many years is whether various carcinogenic agents are active even in very small amounts, or whether there are amounts or concentrations of such an agent below which no effect is produced, or below which the effectiveness drops off out of proportion to the reduction of dosage. The existence of a threshold, or at least of a marked nonlinearity of effect at low dosages, is rather taken for granted in most areas of toxicology, where the degree of general physiological impairment seems to determine whether or not an end point such as death or a persistent pathologic change is produced, and where it is reasonable to assume that essentially complete repair can occur if the insult is removed or if its intensity is low.

It has been thought that a different situation might exist where cancer is the end point. The main reason for this lies in the special nature of malignant disease, which in its natural course leads inevitably to death, yet which ordinarily arises in a small anatomical focus, perhaps in a single cell. On this basis, then, it may be conceived that cancer could arise through a single randomly determined alteration in a cell of the host, which conferred on it the capacity to reproduce itself indefinitely. By analogy to the point mutation in genetics, we can see that a theory postulating a linear relation between the amount of a carcinogenic agent and the probability of a malignant response is allowable even where the respective amounts and probabilities are vanishingly low. The purpose of this article (*1*) is to examine whether such a relation has been verified (as some seem to assume) or indeed whether it seems reasonable in the light of present information.

While a generalized hypothesis of linearity of the carcinogenic response can apply equally to many types of malignant disease and to many agents, perhaps the strongest argument in favor of this hypothesis has been presented by Lewis (*2*) on the basis of several published studies of leukemia induction in man by ionizing radiation. The ensuing discussion will deal mainly with this special case, but it will be clear that many of the considerations presented apply equally well to the more general case of cancer induction by a variety of agents.

There is no question as to whether leukemia may be a result of total-body irradiation, or of irradiation of large masses of blood-forming tissue, at high dosage levels—that is, at levels at or above 10 or 20 percent of the acute lethal dose, where widespread cellular destruction occurs in both lymphoid and myeloid tissues. This has been well established in work with animals and is obvious as well from the human data to be discussed here.

The author is director of the Division of Biological and Medical Research, Argonne National Laboratory, Lemont, Illinois.

The Human Evidence

The data on leukemia incidence in the irradiated populations of Hiroshima and Nagasaki (*3*) suffer from the fact that they have been calculated on the basis of concentric circles at 500-meter intervals from the hypocenters. Within each sector defined in this way, the range of radiation dosages is very large. For the area up to 1500 meters from the hypocenter (that is, the area where dosage to unshielded or slightly shielded persons is currently estimated as 125 rad or above), the evidence for induction of leukemia is plain, and it is clear that the incidence increases the closer a person was to the hypocenter.

In the critical area, from the point of view of this argument—that from 1500 to 2000 meters from the hypocenter—the leukemia incidence has appeared likewise to be increased, although the increment was, in absolute numbers, not more than four or five cases. Such preliminary data as were available until recently (*3*) indicated, in fact, that the increment is limited to the nearest quartile of this area—that between 1500 and 1625 meters—and that those cases seen from the area beyond 1625 meters occurred with a high probability in persons who had acute radiation symptoms (*4*). This would suggest that these individuals received substantially more than the estimated dosage, or else that other factors leading to acute aplastic anemia were of importance in the subsequent development of leukemia. It may be concluded that no increased incidence of leukemia following a smaller dose than 100 rad has been demonstrated. Publication of more recent figures (*5*) shows that the incidence of leukemia within the 1500- to 2000-meter sector equals that in the control sector within one standard devi-

ation and further emphasizes the uncertainties of present dosimetry. The present data are at least as compatible with a physiological mechanism linking leukemogenesis with initial severe hematopoietic damage, or with some other nonlinear relation, as they are with one assuming an effect that is strictly linear with dose.

The best documented evidence of increase in leukemia incidence with increase in radiation dosage is that detailed by Court-Brown and Doll (*6*). These investigators made a painstaking study of patients irradiated over the spine and elsewhere to alleviate the symptoms of ankylosing spondylitis, and the individual doses have been carefully calculated. It is noted that the calculated mean spinal marrow doses show a *curvilinear* relation to leukemia incidence. Something resembling a *linear* relation can be deduced only by discarding those cases in which extraspinal irradiation was also given. The effect of this procedure is to eliminate almost all of the cases receiving a high dosage—those which most clearly demonstrate the nonlinearity of the function. It is indicated that these cases were omitted because high doses elsewhere may have involved other marrow areas; however, since the calculated integral body doses also show a curvilinear relation to leukemia, the reason for this treatment of the data is not at all apparent. Indeed, the authors state that they cannot rule out a threshold but suggest that a linear relation without threshold constitutes a good "working hypothesis."

While the actual data indicate that this working hypothesis is a less probable one than one that assumes a threshold or a nonlinear relation, it is illuminating to make a careful study of the clinical protocols. First, of the 32 cases accepted as leukemia after careful study of pathologic material, only 22 were so certified at death, and another five cases were classed as suspicious but lacking a final positive diagnosis. Many more cases of aplastic anemia were observed within the same range of dosages. Those who have had experience with clinical leukemias will be impressed by the high proportion of equivocal cases. If one is willing to forego the statistical requirement of assigning each case to a single disease category, it is obvious that many of the cases illustrate the unfolding of a sequence of pathologic changes in which a persistent disordered or aplastic state of the marrow is a precursor rather than a consequence of leukemia. This is likewise true of other agents similarly affecting the bone marrow, notably benzol (*7*).

All of the cases of leukemia arising in this series followed doses exceeding 450 r to the spinal marrow, with one exception. In the exceptional case, the leukemia was of the lymphatic type and the patient had been more heavily irradiated in extraspinal areas.

In other series of cases where leukemia has resulted from irradiation, there is no information bearing on the question of linearity. Children receiving treatment to the thymic area have shown an incidence of about 0.5 percent (*8*). This is true in both dosage groups—above and below 200 r. There has been no further breakdown of the dosages, but it may be presumed that all irradiations were severely damaging to thymic tissue, since the purpose of treatment was to produce involution of the presumably enlarged thymus. Cancer of the thyroid is also frequently preceded by thymic irradiation above 200 r (*9*), but it is possible that complicated endocrine interrelationships may be operative in this instance.

It has been noted for some time that American radiologists are more prone to leukemia than other physicians (*10*). The average dose sustained by this group has recently been estimated as about 2000 r delivered over many years (*11*), but no particular distribution of individual dosages can be assumed, and it is certainly not justifiable to use any estimated average dose in an argument concerning linearity unless the distribution can be established. Since the average accumulated dose to radiologists seems to have been far in excess of the single midlethal dose for man, and since the increment in leukemias is much less than that observed in the most heavily exposed Hiroshima survivors, it would seem that a gradually accumulated dose is much less effective than the same dose received at one time. This is in accord with experimental data, and its significance will be discussed later.

The most impressive survey indicating that leukemia may follow rather low single doses of x-ray is that of Stewart *et al.* (*12*). In a partially complete survey of childhood leukemias in England and Wales over a 3-year period, it appears that abdominal radiography during gestation (generally radiographic pelvimetry) about doubles the probability of development of leukemia, and also of various forms of cancer, in the first 10 years of postnatal life. While the fetal radiation doses would be assumed to be small, they are quite variable even in the instances so far reported (*13*), and in a survey of an entire country, they almost certainly cover an even wider range of techniques and dosages, perhaps including a certain number of fluoroscopies. Pending the accumulation of further data (for example, regarding the variables of sex, order of birth, and domicile), it can only be said that these data reaffirm that radiation is mildly leukemogenic, but that they add little to the linear hypothesis. Certain criticisms of the study have been brought forward (*14*), particularly to the effect that radiographic procedures may be based on particular medical indications which may bear some causal relation to leukemia in children. Another recent study (*15*), while not taking into account radiographic pelvimetries, demonstrated that allergic states in the mother (including the use of antihistaminic drugs) predisposed to the development of childhood leukemias.

There has been a formidable increase in leukemia incidence in the United States population in the past few decades; it more than doubled between 1925 and 1940 in all classes (white and nonwhite males and females) (*16*) and continues to increase. The increment certainly is relatively greater than that in the average population exposure to radiation in the same period. A part of this increase is no doubt due to improved diagnosis, since, as was mentioned above, a diagnosis of leukemia is not always simple or obvious. While this steady increase has been loosely attributed to an increase in human irradiation (*17*), there seems to be no doubt that many other potentially leukemogenic agents have likewise had increasing impact on man, none of which (except perhaps benzol) has been seriously considered from the standpoint of possible leukemogenic action. The suggestion has been made (*18*) that, as a result of reduced mortality from infections, persons sustaining damage to the bone marrow are increasingly likely to survive to develop leukemia.

It would appear from the foregoing discussion that, in the only series of data where linearity from zero might be demonstrated (*6*), it has indeed not been shown. It is also apparent that a critical analysis of the data fails to establish any human leukemogenic response below about 100 r, although, on further analysis in detail, the data of Stewart (*12*) might conceivably establish such a response in the special case of the fetus receiving a single, nearly instantaneous dose. Various alternative hypotheses can be constructed which conform to the existing

information as well as, or better than, this one.

There is relatively little reliable clinical information concerning other forms of malignant disease in the same context. The American radiologists, who have shown a considerable propensity to leukemia, have not shown any increased tendency to tumors of bone, although at the voltages used in diagnostic radiography, the bone-forming cells may be expected to receive several times as much ionization as do the soft tissues. Studies of juvenile cancer of the thyroid have shown that it usually occurs in persons who have had previous irradiation of the thymus, which, as mentioned above, entails a dose of about 200 r. In Stewart's studies relating childhood leukemia to diagnostic procedures on the gravid mother, a similar relation was found with other forms of malignant disease occurring before the age of ten.

Experimental Studies

In spite of the extensive work that has been carried out in experimental carcinogenesis, there is remarkably little which suggests the possibility of a linear dose-response relation—the most obvious one to look for—while there are many instances in which the response is clearly not linear. One recent review of the subject, referring to radiation carcinogenesis, states that "none of the animal experiments have indicated a linear relationship between tumour incidence and dose" (*19*).

Among the difficulties encountered in such studies are: that there is a natural "spontaneous" incidence of all or most tumor types; that there is a "latent period" which may be a significant fraction of the life span, and which appears to increase as the dose of the carcinogen is lowered; that induced tumors may continue to develop throughout life; that the spontaneous incidence usually increases with age; and that verification of a single tumor ordinarily requires careful microscopic study of well-preserved material (this is particularly true of the leukemias).

One clear instance of a nonlinear response is that of lymphoid tumors in mice induced by total-body x-ray (*20*). Here the latent period is short (about 100 days) and the response runs its course well within the life span of the species; also, the natural incidence as a function of age is well established. Under these circumstances it has been shown that the number of additional tumors increases more than tenfold as the x-ray dose is increased by a factor of three.

Further evidence of the nonlinearity of this form of leukemogenesis is seen in a study of mice irradiated by doses ranging as low as 16 rem (*21*). While the data are shown only in graph form, it is clear that incidence of thymic lymphomas rises very steeply at the higher doses and cannot be extrapolated linearly to zero. Myeloid leukemia is relatively rare, and the data (involving, apparently, less than a dozen cases at the lower and control levels) seem to allow the possibility of a linear no-threshold function but not to prove it (*22*).

There are no studies of the dose-response relation in chemical carcinogenesis that have been extensive enough to settle the point under discussion. Careful scrutiny of the data of Bryan and Shimkin (*23*) suggests a threshold for one carcinogenic hydrocarbon but not for another, but in neither case were enough animals exposed at lower doses to establish the true nature of the function. Graffi (*24*) has presented data showing a marked threshold when dimethyl-1,2-benzanthracene is painted on mouse skin, while if croton oil is also administered, a linear relation appears at daily doses of between 10 and 100 micrograms of the carcinogen.

Induction of bone tumors by divided doses of strontium-89 was demonstrated some years ago to be markedly dose-dependent (*25*). In this instance the rate of tumor development was found to be proportional to dose and to the time after the end of a latent period. I interpreted these data to indicate that each increment of radiation confers an equal probability of tumor development that is indefinite in time, *beginning after* a latent period which becomes longer as the dose rate is reduced. In a sense, this is a linear response, but in the context of the mutation theory the latent period becomes meaningless, since a simple somatic mutation theory implies equal responsiveness of any single cell receiving a certain point mutation (necessarily basic to a linear response at low doses). If one calculates numbers of tumors at any given time after the onset of irradiation, a markedly nonlinear function is seen.

Perhaps the only recent experiment in which a linear relation is more than remotely possible is that of Bond *et al.* in which mammary tumors (benign and malignant) were induced in Sprague-Dawley rats by doses of total-body x-ray of between 25 and 400 r during the first year of life (*26*). Since these tumors are very common in females of this strain at a year or more of age, and since the numbers produced in this experiment are equivocally small, linearity cannot be proved even within those limits, and the possibility of an acceleration of a normal process has not been ruled out.

Ultraviolet light is consistently effective in the production of skin cancer in man and other animals. Blum (*27*) has analyzed the results of several time- and dose-patterns of irradiation and has failed to demonstrate any responses that fit with a linear hypothesis. The response is markedly time-dependent and requires continued exposure, and its nature indicates rather conclusively that a sequence of radiation-induced changes must take place before a tumor will appear.

For a single-event theory to hold water implies that the response must be independent of dose rate. Lack of dose-rate dependence has been one of the crucial proofs of the linearity of the genetic point mutation. No cases of strict equality of the carcinogenic response at different dose rates have apparently been reported. As a rule, the response drops off with lengthening of the total time of exposure. This is seen clearly in rats exposed to external beta irradiation in single or daily doses (*28*). In the case of lymphoid tumors in mice, the induction rate appears to pass through a maximum when irradiation is distributed over a period of a few days, falling off on either side of this optimal rate (*20*).

There are many examples of the induction of malignant disease through mechanisms which are clearly indirect—that is, where irradiation of a cell can be shown not to be the critical factor. It has been found, for example, that irradiation of the mouse ovary results in ovarian cancer only when all of the ovarian tissue has been irradiated, so that pituitary gonadotrophins are evoked and stimulate this tissue to hyperplasia and, eventually, to abnormal growth (*29*).

A striking example of the indirect mechanism is seen in induction of lymphoma in mice, which, as mentioned above, is clearly not a linear response. Mice in which lymphoma is readily induced by total-body irradiation can be almost wholly protected by shielding part of the body (*30*), or by irradiating the anterior and posterior halves of the body a few days apart (*31*). Since lymphoma can also be prevented by the administration of bone marrow following total-body irradiation (*32*), it seems likely that a prolonged depression of the

whole blood-forming system is more critically necessary to its development than irradiation of the cells. It has, in fact, been noted that while lymphoma can be prevented by thymectomy in certain strains, it may develop in an unirradiated thymic transplant in an irradiated mouse (*33*).

In addition to these and other evidences of indirect physiological mechanisms intervening between tissue irradiation and malignant change, there is a large body of evidence indicating that the malignant transformation occurs after a sequence of "precancerous" stages has taken place. The most widely observed example is in the development of skin cancer, which, in whatever way it is produced, is likely to be preceded by various types of benign atrophic or hyperplastic states; in experimental studies it most often develops in a benign papilloma. It has long been known that in rabbits treated with tar, a large number of papillomas is produced but only a very occasional one proceeds to malignant change. Glücksmann (*34*), studying precancerous tissue changes, has observed that, following local irradiation, there is a long succession of destructive and proliferative changes culminating finally in cancer; this is in contrast to induction of similar tumors by hydrocarbons, where, if the treatment is intensive, the cancer may appear almost at once. It appears to be impossible, by increasing the dose of a radioactive agent, to reduce the latent period of carcinoma or sarcoma below about 6 months (*35*). Many other lines of evidence point in the same direction: the statistical studies of Blum (*27*) on ultraviolet-induced tumors; the pathologic studies of Foulds (*36*) on spontaneous breast cancer; studies on cocarcinogens (for example, croton oil) (37); Tannenbaum's observations (*38*) concerning the different effects of diet in the early and late phases of carcinogenesis; and a number of recent studies on the gradual process by which a tumor develops invasive characteristics. The entire question of the complexity and apparent multistage nature of carcinogenesis has been discussed at length by others, including Huxley (*39*) and Oberling (*40*).

The Somatic Mutation Theory

It has been natural to think of the cancer cell as a mutant of the normal tissue cell. What sort of mutation or combination of mutations it may represent has, however, defied intensive and prolonged study. In the last analysis, cancer is defined by its interaction with the normal tissues—by its "invasiveness" or ability to metastasize in the original host, or to transplant into a genetically nearly identical recipient or into an immunologically inert environment such as the anterior chamber of the eye (these criteria, incidentally, become satisfied only in a relatively late stage of a morphologically identified cancer). Morphologically, it is characterized by variability of cell size and by irregular mitoses; on careful cytological analysis, by aneuploidy and the presence of supernumerary chromosomes.

The unequal mitosis was first clearly recognized by von Hansemann in 1890 (*41*), and Boveri later (*42*) emphasized that this might have significance in the etiology of tumors. The concept of the somatic mutation grew, with increasing sophistication in genetics, and was first spelled out by Whitman in 1919 (*43*). Muller, in a brilliantly concise paper in 1927 (*44*), first suggested a possible relation between the mutagenic and carcinogenic actions of x-rays. In the past 30 years, workers in cancer research have kept the somatic mutation theory under scrutiny, but no definitive test of it has been achieved.

It is important to keep in mind that the somatic mutation theory is amenable to a variety of interpretations. In the sense that it is merely a restatement of well-known facts, it has little meaning to the present argument. Only if it is defined restrictively as referring to a single point mutation or similarly unique event does it imply a linear relation between cancer incidence and the amount of a mutagenic carcinogen. In the event that particular sorts of chromosome rearrangements or a certain combination or succession of mutations are necessary, a linear relation is negated. Careful consideration of the evidence has led to even broader interpretations of the theory—namely, that the critical changes occur through interaction of enzyme-determining genes, plasmogenes, and substrates (*45*). The view that cytoplasmic changes are important is supported by the fact that the chemical carcinogens appear to be fixed to cytoplasmic rather than to nuclear constituents (*46*).

Efforts have been made to find a correlation between mutagenic and carcinogenic potency of various agents and have, in general, met with exceptions in both directions (*47*). The entire matter of the somatic mutation theory has been carefully reviewed by Burdette (*48*), who finds little evidence favoring a single cell-mutation process. The remainder of this discussion, except where otherwise indicated, will refer to the point mutation in a single cell as the carcinogenic determinant, since that concept is necessary to the linear theory.

I have previously taken occasion (*49*) to direct criticism against the somatic mutation theory on the basis of the mutation rates it implies, particularly when animal species of greatly differing size are considered. While the genetic mutation affecting an individual is clearly traceable to an event occurring in a single cell, the somatic mutation which leads to a tumor in an individual would be presumed to have occurred in any of a very large number of cells of the parent tissue. A postulated rate of human leukemia development of around 10^{-6} per year per roentgen (*2*) (since there are perhaps 10^{11} proliferating myeloid cells capable of mutating) yields an estimated somatic cell mutation rate of about 10^{-17} per year (*50*). Similarly, the "spontaneous" cell mutation rate to leukemia on these assumptions must be very low. A little computation shows that if cancer is a result of a particular mutation in a single cell, a local radiation-induced perturbation in a given molecule is extremely unlikely to produce a carcinogenic somatic mutation; or, expressed in older terminology, such a mutation must occur in an infinitesimally small target area (*51*). In more modern genetic terminology, the "penetrance" of such a mutation must be so small as to require some special interpretation.

The situation is still more difficult to rationalize when we consider the implications of the fact that different species, such as mouse and man, have roughly equivalent cancer rates (spontaneous and radiation-induced) but that the number of cells from which cancer presumably can arise differs by a factor of more than 1000. This applies if mutation rates of somatic cells are properly to be calculated per generation of the species; if they were to be calculated on the basis of time, an additional factor of about 30 would be introduced. With reference, for example, to myeloid leukemia, it is apparent that the rates per mouse and per man are the same within an order of magnitude (*52*).

One possible way out of this dilemma would be to adopt the assumption that somatic mutation rates are much lower in man than in smaller, shorter-lived animals. In view of the great structural and functional similarities between somatic cells of the various species, and since no differences exist in the genetic mutation rates (spontaneous or in-

duced), this seems highly improbable. Another possible escape would be to assume that only a certain small number of cells (say one) in a given tissue of any species was capable of undergoing a mutation to cancer. Such circumstances as those, however unlikely, might serve to explain why certain species are able to attain greater size and age span than others. I feel, however, that the burden of proof must rest on those who are attracted to the somatic point-mutation hypothesis because of its superficial simplicity, and that they are the ones to take those difficulties into account.

If we are to accept the rather apparent fact that a large number of cells are potentially capable of mutating to cancer cells, and that therefore the somatic *cell* point-mutation rates must be enormously lower than those encountered in genetic mutations at a single locus, we are led to the conclusion that cancer is a very improbable result of a single mutation and, therefore, that other events are necessary in addition: perhaps one or more additional mutations occurring in the same or nearby cells, or other, physiological determinants. In the first instance the dose-effect relation will be a curvilinear one representing a power function of dose [the data of Court-Brown and Doll (*6*) actually fit a square-of-dose relation much better than they do a linear one]. The species discrepancy might then be explained on the basis that the functions are of a different power—that is, that different numbers of "hits" are necessary to produce cancer in different species; this has indeed been suggested to account for various spontaneous cancer rates in several species (*53*).

Considerable attention has been given recently to the natural age incidence of cancer as well as to that of gross mortality. It has been known for over a century (*54*) that human mortality rates tend to increase exponentially with age, indicating a mathematical function (the Gompertz function) of what may be called the aging rate. In recent years, with advances in medical means of combating infections and other diseases of early and middle life, this function is increasingly evident in vital statistics (*20, 55*). In animals of shorter life span, the mathematical function remains the same but the time scale is shortened, so that the doubling time of the mortality rate is about ten years in man and 100 days in the mouse.

A similar age-incidence function applies to many diseases, including the various forms of cancer (*55*). In the latter case, it has been noted that there is an early peak in childhood, the height of which varies with the tumor type (this is essentially the only component in some neuroblastic tumors and in Wilms' tumor of the kidney), suggesting that there may be two basically different mechanisms of "natural" carcinogenesis. It is apparent that the cancer curves decline from the exponential slope in extreme old age; this may be an artifact of diagnosis or it may represent an effect of senility on the process; it has also been pointed out that the curves may better be fit to a power function of time, as if a multiplicity of events is necessary (*53*).

It is difficult to explain the age incidence by a single-mutation mechanism of carcinogenesis; this certainly cannot be done if we are to assume that radiations (or similarly acting chemical agents) are totally responsible, through such a mechanism, for forms of cancer in which the exponential age incidence is observed. One possible mechanism involving mutational change has been suggested by Armitage and Doll (*56*), who postulate that an initial change gives rise to a clone of exponentially growing cells which are subject to a further, carcinogenic change. This, if applied to radiation, would imply an exceptional effectiveness of widely spaced dosages, which does not appear to have been observed. Other explanations of the natural age incidence based either on an exponential or a logarithmic curve have also postulated multiple independent events (*57*).

Alternative Hypotheses

It has already been made clear in this discussion that a linear theory resting on the somatic mutation is not valid if more than one mutation, or if some nonlinear phenomenon such as a chromosome rearrangement, is necessary. This may be generalized by saying that a linear theory is valid only if a single factor in the process is linearly responsive to the carcinogen (for example, radiation), while all others (if any) are quite independent of it. Such complications may indeed exist in radiation mutagenesis in the mouse, where neither dose nor dose rate shows a clear linear relation to genetic mutation rate (*58*).

Cocarcinogens. There is much to suggest, in experimental carcinogenesis, that "latent" tumor cells are produced by one process and brought to a malignant state by a cocarcinogen The most potent such agent is croton oil. In the mouse, this agent brings to rapid fruition many tumors that are potentially created by a chemical carcinogen (*37*). It has been found that croton oil abolishes the threshold which is observed when only the carcinogen is applied (*24*). On the other hand, repeated applications of the carcinogen have been more effective in producing malignant tumors than a single application followed by the cocarcinogen (*59*). Where croton oil treatment follows a radiation exposure, only an increase in the number of benign papillomas has been observed (*60*).

Role of cell division. It can be envisioned that a number of cell divisions may be necessary in order for a carcinogenic mutation to manifest itself; such phenomena have been observed in other fields of genetics. This could explain the rather high frequency with which malignant changes occur in tissues that are cultivated over a period of months (where the mass of tissue is small, but where more successive cell generations occur than in the achievement of the cell mass of an adult).

In this instance, it will be noted that massive destruction of tissue results in regeneration of cells and that this process is observed repeatedly during the "latent period" following carcinogenic irradiation of tissue. This is difficult to fit to a linear hypothesis. In the first place, Puck and Marcus have demonstrated that cell death is not linear but is better described by a two-hit curve (*61*); also, the number of cell generations required in repair would more or less be an exponential function of the relative amount of destruction.

Carcinogenic potential of a single cell. It may be observed that a single cancer cell is unlikely to give rise to a tumor. This is dramatically shown by the extraordinary frequency with which cancer cells are seen in relatively small samples of blood draining a human tumor—for example, in 10-milliliter samples from over 20 percent of patients, including many which are not showing metastases (*62*). In highly autonomous experimental tumors, under favorable conditions, single cells may transplant to give tumors, but under most conditions large numbers of cells must be inoculated for a "take."

Physiological environment. It has been generally believed that the tissue environment is important in determining cancer cell growth. This concept has many facets. The proliferation of single cells in tissue culture, for example, requires that they be closely confined, or

that they be explanted with a large number of other cells, or that they be in a "conditioned" medium in which other cells have been cultivated. Again, as was described many years ago by Willis (*63*), there is little evidence from detailed histologic work that would lead one to believe that cancer arises in a single distinguishable cellular focus, since it is usually multicentric in its earliest visible stages. Biochemical studies have led Warburg (*64*) to suggest that the tumor arises in some way adaptively to an environment in which oxidative processes are interfered with. Experimentally it has been found that small tumor inocula take more readily in altered tissue, such as in the liver damaged by chloroform (*65*), while experiments employing skin transplantation have shown the same thing in the converse: carcinogenically treated epidermis fails to produce tumors when it is transferred to a fresh site (*66*).

While these observations are somewhat varied and point in a number of directions (and there are many more such), they all point away from the simple concept of a single mutation operating free of other influences which depend on the carcinogen. To take radiation as an example, a visible disorder of tissue architecture and of its vascular supply is universally characteristic of those dosage levels at which cancer is an observed end result. It should not be forgotten that in a number of other situations where such disorder is the chief recognizable change—as, for example, following thermal burns—cancer frequently arises.

While the concept of a multiplicity of single mutation-like events leads necessarily to a nonlinear relation between dose and cancer incidence, the added concept of a state of tissue disorder as a requirement of tumor appearance implies that a true threshold can occur. There seems to be no direct evidence of any sort that can rule this out.

Enzyme deletion and similar mechanisms. Considerable evidence has been brought forth recently which indicates that cancer may very well not be due to a gene mutation mechanism at all, but to a special situation determined by cytoplasmic (that is, plasmagene-dependent) conditions leading to deletion of certain enzyme-forming systems (*67*). Evidence for this is found in the fact that many chemical carcinogens are fixed to cytoplasmic proteins; that the enzyme patterns in tumors are characterized mainly by various deficiencies; and that changes in enzyme patterns—in particular, development of new pathways—can owe their origin to shifts in the concentration of various substrates. This condition can occur through known positive and negative feedback systems. Perhaps the most important of these involves pathways, only beginning to be defined, by which the formation of thymidine is kept under control (*68*). A failure of the feedback mechanism which normally retards thymidine synthesis might be sufficient to give rise to cancer as it is clinically recognized and defined. Such a mechanism of carcinogenesis would explain the necessity for a particular substrate concentration, hence for a group of potential cancer cells or of a specially abnormal tissue milieu. It would likewise predict—unless such systems are as unique in each cell as are single genes—a multiplicity of "hits," involving in addition, perhaps, a competition between normal and abnormal plasmagenes for supremacy. Haddow (*69*) suggests a nuclear site for the development of enzymatic changes or deletions altering growth control, perhaps in the heterochromatin, and Green (*70*) has developed evidence for a theory that the loss may be of certain immunologic identifiers. While a single-event process might be consistent with some of these mechanisms, I feel that many of the considerations given above cast great doubt on this possibility.

The virus theory. Brief mention may be made of the theory, for which there is some experimental evidence, that there is a provirus which may, through action of a carcinogenic agent, be altered to produce a tumor agent in the cytoplasm. Such viruslike agents include the milk factor and the leukemia agent (*71*). The possibly analogous production of infective agents from lysogenic bacteria has been shown by Marcovich (*72*) to be linear with a large range of radiation dosages. Again, the great rarity of carcinogenesis as a cellular change appears to be strong evidence against accepting this as a single-hit cause of cancer; also, the type of leukemia in which this sort of agent has been demonstrated, the lymphatic leukemia of the mouse, is the most notorious instance of a nonlinear radiation response.

Discussion

It has been suggested that strontium-90 from fallout might be linearly responsible for a very low (but in absolute numbers, appreciable) incidence of leukemia. It has been further suggested that very low-level increments of carbon-14 might (due to its 5000-year half-life) result, in many thousands of years, in calculable, if not determinable, numbers of leukemias. From the foregoing discussion it is deduced that this seems most improbable. Moreover, strontium-90 can, in man, affect only a very localized part of the marrow, and at a dose rate which is extremely low.

This review has necessarily included only a small part of the literature pertinent to this subject; the evidence offered against linearity at low doses must be taken only as illustrative, while the evidence in its favor has been discussed rather completely. With present experimental evidence failing to demonstrate linearity even in genetic mutations in the mammal, it would not seem reasonable to give undue credence to linearity in the much more complex matter of cancer production. The reader is encouraged to examine some recent thoughtful reviews on the subject (*73*) before accepting a simple theory of carcinogenesis.

Summary

1) Present data on human leukemogenesis by radiation fail to indicate a linear relation between dose and effect. Because data are scanty, such a hypothesis cannot be ruled out statistically, but it is less probable than a nonlinear or threshold relation.

2) Other instances in which carcinogenic agents have been examined from the standpoint of dose and dose-rate relations show many clear instances where the relation is nonlinear and none in which linearity is unquestionably demonstrated.

3) Theoretical consideration of the probability that a single critical molecular event, such as a mutation, will give rise to cancer indicate that a malignant change must be an extraordinarily improbable result of such a perturbation. It is also very difficult to reconcile this mechanism with the rather comparable spontaneous and induced-cancer incidences in species with greatly different numbers of cells.

4) Any scheme in which multiple events caused by the carcinogen are required to produce a tumor is incompatible with a linear relation, while, if a disordered state of tissue is an important factor, a true threshold may even occur. There is much evidence, from cancer research of all sorts, indicating that one or both of these conditions is involved in the carcinogenic process.

References and Notes

1. Much of this material was originally proposed as a letter to the editor; I have elected to expand it in view of the importance of the subject and the accumulation of new documentary material. This work was performed under the auspices of the U.S. Atomic Energy Commission. I wish to emphasize that I alone am responsible for the opinions herein expressed.
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CURRENT PROBLEMS IN RESEARCH

Muscle Research

It is one of the oldest and newest lines of biological inquiry, promising an insight into the nature of life.

Albert Szent-Györgyi

If science is the art of measuring, then muscle has no equal as a material in the study of life, for there is no other tissue whose function is connected with equally extensive and intensive changes in chemistry, physical state, energy, and dimensions. This is why physiology, up to the turn of the century, was mainly muscle physiology. After muscle had been pushed into the background by enzymes and hormones for a while, the development of modern physical methods once more turned attention toward it with its macromolecular organization and its "mechanochemical coupling" (the conversion of chemical bond energy into work).

Muscle also has a strong appeal to the medically minded. The heart and the uterus both are, in a way, but bags of muscle, and our blood pressure is regulated by muscles that determine the lumen of our smaller blood vessels.

The function of muscle is to create motion. There are many sorts of motion, and thus there are many sorts of muscles, even if the basic principles on which they are built may be identical. A muscle cell or fiber is a very complex system, and the unit of its function, the twitch, is a very complex cycle. Hence, "muscle research" covers a wide field of

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inquiry. Fortunately, research is simplified to some extent by the fact that energy production and energy consumption are separated. This separation enables the researcher to work on one of the two processes independently. What is driving the muscle machine is, according to our present knowledge, the free energy released by the splitting of the terminal "high-energy phosphate-bond, ~ P," of adenosine triphosphate (ATP), which is created at the expense of fermentation and oxidation. Oxidative phosphorylation is linked to the mitochondria, while contraction is the function of the contractile filaments.

There are many approaches to muscle. We can inquire, for instance, into the physical changes accompanying contraction, measuring heat production or changes in elastic properties, as A. V. Hill and his associates have done. We can inquire into the nature of the single parts of the contraction cycle, asking how depolarization is produced on the muscle membrane, how this depolarization is propagated, how it triggers the function of the contractile matter inside the fiber, and how the contracted muscle returns to its resting state. We may inquire into the nature of the contractile material and the changes which it undergoes in contraction and subsequent relaxation, and we may inquire into the feedback mechanisms which adjust motion to the physiological requirements. Since each of these partial processes represents a more or less self-consistent field of inquiry, it is impossible to cover all of them within the boundaries of a short article. Accordingly, I shall limit myself to one aspect only, one to which most of my personal experience relates: the problem of the mechanochemical coupling and the nature of the main contractile protein, myosin.

Early Work on Myosin

Myosin has been known for almost a century, having been discovered by W. Kühne, who showed that a great amount of a protein can be extracted from muscle by a strong salt solution. This protein precipitated on dilution of the salt present and was found in the 1930's by Edsall, Muralt, H. H. Weber, and others to consist of rod-shaped molecules. When I embarked on muscle research two decades ago it became increasingly clear that what was driving contraction was the ~ P of adenosine triphosphate. Engelhardt and Ljubimowa (*1*) had just discovered that myosin could split this bond and thus release the energy which it needed for its contraction. The idea of a "contractile enzyme" was most exciting. None of us had much doubt, then, that contraction had to be some sort of a folding, elicited in the myosin rodlets by the ATP molecule at certain points, and we were looking forward to the possibility of describing this reaction soon by a simple chemical equation.

The only trouble was that myosin would not contract outside the body. My associates, Banga and Straub, and I showed (*2*) that this failure was due to the fact that the contractile protein was not myosin but actomyosin, a complex of myosin with a hitherto unknown protein, "actin." About the same time Schramm and Weber (*3*) showed "myosin" to be dishomogeneous in the ultracentrifuge. Under the electron microscope (Ardenne and Weber, *4*) the faster sedimenting fraction was found to consist of filaments which were, evidently, filaments of actomyosin.

In the resting muscle there seems to be no interaction between actin and myosin, the formation of actomyosin being brought about by "excitation." The association of actin and myosin goes hand in hand with the increase in elastic modulus which characterizes the "active state" of A. V. Hill (*5*). Once it has been formed in the presence of physiological concentrations of ATP and ions, actomyosin has to go over into its contracted state. The energy spent in this process can be used to lift a weight—that is, to do work.

What made actin exciting was the fact that it allowed us to produce and study motion and contraction in vitro, and bolstered our hopes that soon we would know all about the process. If ATP was added to actomyosin in the test tube, the actomyosin underwent violent physical changes which consisted in the shortening of its filaments and the loss of its hydrophilous character. The analogy between these in vitro reactions and muscular contraction could be brought closer by showing that a muscle, thoroughly extracted with glycerol, is still capable of contracting and developing maximal tension on addition of physiological concentrations of ATP (*6*). (Glycerol destroys the finer mechanisms but leaves actomyosin intact.) So the conclusion could be drawn that muscular contraction, essentially, is an interaction of actin, myosin, ATP, and ions. I will omit the discussion of actin and limit myself to myosin.

Complex Nature of Myosin

The first experimental evidence that the situation was not as simple as we believed and that myosin is not a homogeneous rodlet was obtained by Gergely (*7*) and Perry (*8*), who showed that trypsin decreased the viscosity of myosin solutions without decreasing its ATP-ase activity. The myosin, thus treated, could be separated into two fractions, only one of which showed enzymic activity. After studies pursued with Mihalyi (*9*), the final analysis of this change was given by A. G. Szent-Györgyi (*9*), who showed that the "myosin molecule" is disintegrated by trypsin into six subunits, *meromyosins,* which were shunted in a row, in series. There are two different kinds of such subunits. One kind was thicker and sedimented faster than the other and was, accordingly, called "H" (heavy), while the other was slender and had a lower molecular weight and was called "L" (light). The H meromyosin had the full ATP-ase activity of the whole myosin molecule and interacted with actin, while the L seemed to be involved in shortening. The nature of the links holding the meromyosins together has not yet been cleared up definitely. All the same, these findings made it certain that the myosin particle is not a homogeneous rodlet but consists of different parts with different structures and functions. The L meromyosin has a high, the H a low, α-helix content (Cohen *et al.*, *10*). That these subunits are, in one way or another, preformed in myosin is also shown by their different amino acid turnover numbers (Velick, *11*).

The situation was somewhat simplified by Laki and Carroll's (*12*) finding that carefully extracted myosin had only half of the previously accepted molecular weight; "old myosin" was thus a dimer formed in vitro after extraction. As far as its dissociating action on actomyosin is concerned, ATP seems to react with myosin in stoichiometric proportions (Hanson and Mommaerts, *13*). To compensate for this simplification, it was found that the meromyosins themselves are built of a great number of much smaller subunits into which they disintegrate if they are acted upon by urea. The L type disintegrates completely, the H partially (A. G. Szent-Györgyi and Borbiro, *14*). The molecular weight of these sub-subunits, "protomyosins," is about 1/100 that of myosin. What is disturbing about this finding is the fact that urea is known to split hydrogen bonds only, leaving covalent bonds intact. If

we define a molecule as a structure with a covalent backbone, then the "myosin molecule" is no molecule at all but a complex system of small units held together by secondary forces, like H-bonds, van der Waals attractions, or dipole moments.

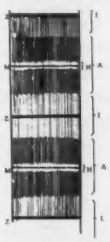
Function and Chemistry

As a rule, new knowledge leads to a better understanding. With muscle, things seem to go in the opposite direction, and one may ask whether the real difficulty does not lie in an inadequacy of our basic concepts. Present biochemistry stands under the domination of classical chemistry, according to which two molecules must come into bodily contact to be able to interact. This woud mean that the ATP molecules can induce changes in the contractile protein only at the points at which they are bound and split. The fact that only the H meromyosin splits ATP, while it is the L which seems to be more directly involved in contraction, suggests the inadequacy of the classical concept, making some sort of a migration of energy seem likely. This calls to mind the case of the *Bacillus proteus*. This bacterium has long flagellums, about as long as a sarcomere. These flagellums move the bacterium by means of the undulatory motion passing along their whole length. According to their x-ray spectrum, as shown by the studies of Astbury, Beighton, and Weibull (*15*), these very thin, threadlike structures are closely related to myosin and have about the same diameter as the contractile filaments of muscle. Thus, in them we see "biological movement stripped to its barest essentials." Since these flagellums are too thin to allow us to suppose that circulation takes place inside them, the energy which moves them must be fed into them at their basal end and then, somehow, must migrate along their length. Perhaps we have taken a much too narrow view of life in trying to explain all its reactions in terms of classical chemistry. In order to understand we might have to descend from the dimension of macromolecules to those of electrons, from classical chemistry to quantum mechanics, taking into account factors such as molecular excitations, the resonance transfer of their energy, solid-state physics, the electromagnetic field and its perturbations, long-range water structures, and, possibly, proton conduction. Everything seems possible at present. Our knowledge of muscle is in the liquid state.

Function and Structure

Looking out for some more solid hold, one can try to correlate the known chemical data with the classical microscopic structure of muscle. Such an attempt was made lately by Holtzer and Marshall (*16*), who applied Coons' (*17*) "fluorescent antibody method" to muscle, injecting the various muscle proteins and their subunits into rabbits and then making visible the immune bodies thus produced by coupling them with a fluorescent dye. These workers found that the different immune bodies were bound differently by the different parts of the sarcomere. The "myosin antibody" was bound by the A-band. This finding supported earlier findings (Amberson, *18*; Hasselbach, *19*; Hanson and Huxley, *20*) that myosin is located in the A-band. The "L-antibody" was bound by the lateral parts of the A-band, while the "H-antibody" was bound by the narrow M-band, lying in the middle of the sarcomere, suggesting that this band is its location, and there may be no such thing as myosin in muscle at all. What we called "myosin" might have been an aggregate of meromyosins formed after their extraction.

Another approach was opened by the polarization microscope of Shinya Inoué (*21*). This instrument, with its high resolution and clean polarization optics, reveals new structural details and shows new cross bands. It also indicates that the A-band contains a relatively great quantity of a structural protein which is neither myosin nor actin and which seems to be identical with the "X-protein" (*22*). The microscope also shows that muscle fibrils from which myosin has been extracted bind H meromyosin with preference in the M-band.



The muscles which move our body consist of fibers of the dimension of a human hair. Under the microscope (schematic representations above) these fibers are found to be built of darker, denser, doubly refractant segments (the anisotropic "A-bands"), and lighter, less dense segments with poor double refraction (the isotropic "I-bands"). In the middle of the I-bands are the "Z-membranes." The segments enclosed by two Z-membranes are called "sarcomeres." In the middle of the A-band there is a thin membrane, the "M-membrane," delimited on either side by a narrow zone of small density, the "H-band."

In considering the problem of correlating structure with function and chemistry, one's thoughts naturally turn to the electron microscope, which extended the domain of morphology into macromolecular dimensions. The first attempt on this line is linked to the names of Hall, Jakus, and Schmitt (*23*), who showed that the muscle fiber, essentially, is a bundle of a great number of thin filaments which do not bend or fold in contraction. New details were revealed lately by the admirable pictures of H. Huxley (*24*) which show the presence of two kinds of filaments in cross-striated muscle. There are thicker "primary" filaments, located in the A-band, and twice as many thinner "secondary" filaments reaching from the Z-band to the H-band. In cross sections the thinner filaments were found to surround the thick ones in a hexagonal array.

Sliding Filaments

On stretching, the two kinds of filaments were found to be sliding past one another, making the H-zone and I-band wider. Building on these observations, Hanson and Huxley (*25*) proposed a new theory of contraction according to which what happens in this process is the opposite of what happens on stretching: the secondary filaments are pulled in between the primary ones with a consecutive gradual narrowing of the I-band, which disappears altogether when the Z-membrane reaches the A-band. A. F. Huxley's (*26*) motion pictures of living muscle strongly plead for this mechanism of contraction, which explains also the puzzling fact that there is no change in x-ray periodicities in initial states of contraction: the muscle shortens but its filaments do not.

No doubt, this theory signifies an important step in the study of muscle. It gives a clear picture of the mechanics and the morphological changes taking place in the contraction of cross-striated muscle, offering a solid foundation for further discussion. But do we really understand muscle now? Far from it; muscle has remained just as much a mystery as it was before. We still do not know what happens when ATP is split and how its energy is, eventually, converted into the pull exerted on the secondary

filaments. The in vitro reaction of actin, myosin, and ATP shows that there are interactions between these substances leading to violent physical changes. Though physical (A. F. Huxley, *27*) and chemical (H. H. Weber, *28*) theories are not lacking, the nature of these interactions is still unknown. They represent the primary happening and form the core of the problem of muscular contraction. Within the framework of the macromolecular arrangements of cross-striated muscle, they cause the secondary filaments to be pulled in between the primary ones, but if this "pulling in" is all there is to it, then shortening should stop at 30 to 40 percent—as soon as the Z-membranes reach the A-band. All the same, muscle can go on shortening up to 80 percent, producing tension all the time. These high degrees of shortening, in cross-striated muscle, may not be physiological, corresponding to the "delta state" of Ramsay, in which changes begin to be irreversible (*5*). All the same, for the theory they are of prime import. Smooth muscles which have no cross bands, and, accordingly, no periodic double array of filaments, also contract up to 80 percent, though they do so at a slower rate. Similarly, actomyosin filaments can contract under the influence of ATP up to 80 percent, though "sliding" makes no sense at all here. So it seems that the sliding of filaments is linked to the specific steric arrangements in cross-striated muscle, where this sliding makes rapid shortening possible, being the secondary consequence of changes which we fail to understand.

Conclusion

So we can sum up by saying that we still do not understand muscle and do not know how ATP is driving it. It may be true not only that our outlook on biological action is too narrow, but also that our knowledge of muscle structure is too incomplete. Important structures, such as the "endoplasmic reticulum" (Porter and Pallade, *29*), have been discovered lately, and there is no reason to believe that this structure is the last unknown. Important protein fractions (*22*) wait for identification, while other fractions, such as Bailey's tropomyosin (*30*) have not yet been fitted into the muscle machine. The dimensions indicate that the myosin filaments are many molecules thick. So we have to suppose that, just as protomyosins have to join in a very specific way to form a myosin molecule (if there is such a substance at all), so the myosin molecules have to join in a very specific way to build a filament —structural details, without the detailed knowledge of which we can hardly hope to understand function. The painstaking and extensive application of current methods may yield a great deal of important new information, but it is possible that entirely new approaches are needed. Such new approaches are being opened in various quarters. Koshland's (*31*) application of the isotope techniques has already led to surprising new data. The magnetic anisotropy of muscle, discovered recently by Arnold, Mueller, and Steele (*32*) in my laboratory, may lead to new clues.

There is a certain urgency about solving all these riddles, for only a better understanding of muscle can enable us to cope with its disorders, which cause so much suffering. The number of dystrophic patients in this country alone goes into the hundred thousand, and so does the number of lives lost because of hormonal disturbances of the membrane activity of uterus muscle cells (Csapo, *33*). We can hope that a better understanding of muscle will not only spare human suffering and frustration but that it will bring us closer, also, to the understanding of the basic principles on which life is built.

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News of Science

Second United Nations International Conference on the Peaceful Uses of Atomic Energy

During the first 13 days of this month scientists from 69 nations met in convention in Geneva, Switzerland, to discuss the peaceful uses of atomic energy. The conference, called the largest assemblage of natural scientists ever convened, followed by 3 years the first such international meeting, which also met in Geneva. Behind both meetings is the historic speech given 8 December 1953 by President Eisenhower. Speaking before the General Assembly of the United Nations, the President pledged the government of the United States to find ways by which "the miraculous inventiveness of man shall not be dedicated to his death but consecrated to his life." The member nations of the U.N., acting in concert, translated this resolve into a continuing international program.

Scope

The formal program of the convention called for 12 general sessions, 6 evening lectures, and 85 seminar-like small meetings. The seminar schedule, which included 16 free periods to be used as the participants saw fit, was arranged on a five-part, or series, structure. Major aspects of atomic energy discussed in the series were (i) physics, (ii) reactors, (iii) chemistry, (iv) isotopes and biology, and (v) raw materials, metallurgy, and reactor technology.

A comparison of the 1955 and 1958 conventions reflects the growth of the atomic energy field. Although there were three fewer nations in attendance at the later meeting, the number of individuals present jumped from 2900 to more than 6300. The number of technical papers submitted is more than two times greater than the 1955 figure, with the result that there will probably be 34 volumes in the published proceedings.

Results

The major results of the conference, which was designed to facilitate the exchange of information between scientists working in the field of atomic energy, follow.

Fission. Fission power plants have already turned out hundreds of millions of kilowatt-hours of usable electricity. By 1970 nuclear stations will have at least 15 million kilowatts of electrical capacity—some 50 times as much as at present. The cost of nuclear power is expected to fall "well below" that of conventional power by the late 1960's in the United Kingdom, and nuclear power will be competitive with conventional power in other countries between 1963 and 1973.

Fusion. Papers indicate that "remarkable progress" is being made on a very broad front in the problem of fusion power. However, speakers estimated that it would take 10 years to reach the "break-even" point in experimental devices (the point at which the energy turned out equals the energy fed in), plus an additional period to develop machinery on an industrial scale.

Propulsion. A "hopeful" outlook for nuclear-propelled ships was indicated by reports on the U.S.S.R.'s icebreaker *Lenin*, launched last year, and the United States' merchant ship *Savannah*, now under construction. Commercial nuclear aircraft propulsion seems much further away, but experiments with small nuclear systems potentially useful in aircraft were described.

Isotopes. Radioactive isotopes were reported serving around the world as new tools in medicine, agriculture, industry, and basic sciences. Their use was reported to be saving industry $400 million a year in the United States and 1000 million rubles a year in the Soviet Union. In medicine, the use of isotopes for diagnosis and treatment was described as "one of the brightest and most exciting developments of modern science."

Hazards. Study of some of the hazards associated with the atomic age revealed that nuclear power reactors had been performing safely, with few disturbances and no danger to personnel, and that it was possible to "see daylight" in the problem of safe disposal of radioactive wastes.

Legal problems. New international agreements will be needed to deal with problems raised by patent laws, prospecting, international collaboration, mobile reactors, the disposal of wastes in the oceans, and possible damage beyond national boundaries as a result of reactor incidents.

Exhibition

In conjunction with the conference, a 20-nation exhibition of the peaceful uses of atomic energy ran concurrently on the grounds of Palais des Nations. In a temporary building erected between the Palais and Lake Geneva many aspects of current work in atomic energy were demonstrated. An operating nuclear reactor, laboratory devices, flow charts, uranium-prospecting vehicles, and a traveling laboratory were among the exhibits.

The United States offered the largest display and had four major sections dealing with basic sciences, life sciences, fission reactors, and fusion research. The exhibition, which was open to both the conferees and the public, drew an attendance of 100,000 persons during the 15 days it was open. It closed Monday, 15 September.

Removal of Secrecy

Most auspicious circumstances surrounded the opening of the convention. Just prior to the first of the month announcement was made that the United States, Great Britain, and the U.S.S.R. had removed all security restrictions on their thermonuclear research.

The action, widely applauded by the conference participants, set the tone of the international meeting. The American scientist who said, "This is pure joy to be able to talk freely," spoke for most participants. Many examples were found in which work done in secrecy in one country was confirmed by work done in another. One case, announcement of proof that pi mesons degenerate into electrons, a matter that had been under study for 23 years, moved one scientist to dance a jig in the corridor of the Palais.

Future Meetings

As at the first conference in 1955, the participants at the Second International Conference on the Peaceful Uses of Atomic Energy considered the possibility of future meetings. Among participants and observers the conviction seemed widespread that the rapid growth of the atomic energy field had resulted in the conferences becoming unwieldy and impractical. Despite the elaborate organizational structure, many scientists found themselves unable to keep up with the flow of information that came out of the numerous sessions. Further, they found that there was inadequate time for informal meetings among the men working in various nations on similar problems.

A commonly expressed view was that future conferences should be held at more frequent intervals and on more spe-

cialized topics. Despite these views, the U.S. delegation suggested a third meeting in 1961. The matter can be expected to be a topic of discussion during the General Assembly session on the United Nations which is currently convened in New York.

Publication of Proceedings of the United Nations Conference on Peaceful Uses of Atomic Energy

The U.N. has announced the scheduled publication of the various reports and statements made at the conference.

The proceedings of the conference will constitute the means by which the information will be made available throughout the world. The only complete edition, which will be in English will consist of the following:

1) Material relating to the objectives and operation of the conference.

2) The record of all sessions. There was a series of plenary meetings and five concurrent sessions, when approximately 600 selected papers were orally presented and discussed.

3) The complete text of all papers submitted to the conference (approximately 2200).

4) A detailed index volume (subject, numerical, and author.) This is an important and useful addition to the published proceedings.

Two new subjects discussed at this conference were "controlled fusion" and the use of nuclear power for purposes other than the generation of electricity, as, for example, its application to marine propulsion. Further details on these topics are available from U.N. information sources.

While the Proceedings of this conference will be of direct value primarily to the scientist, their importance reaches far beyond the purely scientific interest. Papers on finance, banking, health safety, education, and many other aspects of this question will be of special interest to all whose lives and interests involve atomic energy in its broadest sense.

The complete English edition is expected to consist of 34 volumes. They will be produced by letterpress with an 8½-by-11-inch page size; the volumes will probably average 500 pages each and will have a distinctive cover design and dust jacket.

The first volumes will be available in December 1958, and the last volumes are expected off the presses by July 1959. To insure maximum speed in publication, the work of printing has been assigned to printers in several countries in Europe and North America.

Copies of each volume will be mailed to subscribers as soon as they become available.

The average retail price of the English edition of the proceedings will approximate U.S. $15 per volume, or the equivalent in other national currencies; the regular price for the full set will therefore approximate $510.

In a special prepublication offer the United Nations and local bookstores will now accept orders for the complete English edition of 34 volumes at the special price of $435. For this prepublication price, all orders must be received by the United Nations prior to 30 November 1958. In addition to the very substantial economy achieved, prepublication orders will be given priority.

Two payment methods are available.

1) Full payment may be made of the total prepublication price for the complete English edition of $435 or its equivalent in other currencies; for fully prepaid orders no postage will be charged.

2) Those who prefer longer term payment arrangements are required to deposit 10 percent of the prepublication price ($44 or the equivalent in other currencies). Thereafter, monthly invoices covering the full price of volumes sent during the month must be paid as they are received, until the full prepublication price has been paid; the balance of volumes remaining will then be sent.

Readers who do not wish to subscribe to the full series may record their particular field of interest on the order cards provided by the U.N.; for volumes which fall within the particular subject indicated, further particulars will be sent as soon as they are available. The special prepublication terms are available only to subscribers to the complete series.

Abridged editions in French and Spanish will be published by the United Nations. They will consist mainly of the papers presented orally (approximately 600), the papers submitted in the language of the edition, and a selection of other papers. Each of these editions is expected to comprise 15 volumes, and a prepublication price of $190 is available until 30 November 1958.

Heisenberg Theory

The mathematical formulation of a "uniform field theory" developed by German physicist and Nobel Prize winner Werner Heisenberg was criticized recently at a meeting in Geneva of about 200 physicists from the East and West. Wolfgang Pauli of Switzerland voiced doubts about the accuracy of the mathematical computations on which the theory was based. He said that although this must not necessarily prejudice the conclusions drawn by Heisenberg, the theory nevertheless lacks power of proof. Marvin Goldberger of Princeton University commented that "The idea of the theory is highly admirable, but my personal feeling—and that of many other physicists here—is that the mathematical methods used by Heisenberg to arrive at specific numeral predictions must be regarded as being doubtful."

Support for Academic Freedom Work

The American Association of University Professors has announced receipt of a grant from the Jerome Levy Foundation of "no less than $5000 a year," for a 5-year period, the money to go into the association's Academic Freedom Fund. A chief use of the grant will be to give temporary aid to the professor who is discharged or suspended without pay in apparently clear violation of principles of academic freedom, and who is particularly handicapped in making his defense because he lacks money to live on. In addition, the fund will be used at colleges or universities where a general crisis threatens the academic freedom of a whole institution, and where faculty members rising to meet that threat need financial support.

In a statement to the press, William P. Fidler, AAUP general secretary, pointed out that defense of academic freedom is basically the safeguarding of professors in the performance of their work. He recognized that the objective and dispassionate nature of teaching and research will sometimes be misunderstood by an excited public opinion, and that in its extreme form—when the excitement is about evolution, loyalty oaths, or racial segregation, for example—public opinion can become a tyranny. It is then time, Fidler said, to turn to the AAUP's 1915 Declaration of Principles, which describes the nature and function of a university:

"It should be an intellectual experiment station, where new ideas may germinate and where their fruit, though still distasteful to the community as a whole, may be allowed to ripen until finally, perchance, it may become a part of the accepted intellectual food of the nation or of the world. Not less is it a distinctive duty of the university to be the conservator of all genuine elements of value in the past thought and life of mankind which are not in the fashion of the moment. . . . One of its most characteristic functions in a democratic society is to help make public opinion more self-critical and more circumspect, to

check the more hasty and unconsidered impulses of popular feeling, to train the democracy to the habit of looking before and after."

The Board of Advisers of the Academic Freedom Fund will be: Bentley Glass of Johns Hopkins University, Robert K. Carr of Dartmouth College, Ralph F. Fuchs of Indiana University, and Edward L. Hutton and S. Jay Levy of New York City.

Thermophysical Properties Research Center

The Thermophysical Properties Research Center at Purdue University was started in January 1957 with the ultimate goal of becoming a world center for the collection, analysis, correlation, and dissemination of thermophysical properties information and of providing facilities for research to fill in the gaps in the world knowledge of these properties. The center is under the direction of its originator, Y. S. Touloukian, a member of the staff of the School of Mechanical Engineering. It is housed in a small two-story building that stands between the School of Mechanical Engineering, which administers it, and the Statistical Laboratory, without whose digital computer, magnetic tapes, and other data-processing equipment the organization could not function, for it is essentially a mechanized operation. For example a machine method of abstracting scientific articles should soon be in use. The machine scans a printed page and selects and prints only the sentences relating to a specific subject, thus producing an abstract in the author's own words.

The staff of the center consists of seven scientists drawn from the schools of mechanical engineering, chemical and metallurgical engineering, chemistry, and physics. The initial financial needs of the center have been met by some 20 industrial organizations known as founder sponsors, each of which has agreed to make an annual contribution for 3 years.

The number of founder sponsors will be increased by at least 50 percent before the end of this year. Firms may join the group of founder sponsors up until the end of the first 3-year period, which expires 31 December 1959, after which no more will be accepted.

The center's operation is conceived as a continuous program to serve economically all needs in the field of thermophysical properties information, in contrast to a series of costly "crash programs" on individual problems. Therefore, the objective has been to receive small contributions from many firms—the minimum for a founding sponsor being $2500 per year and the average for all founding sponsors thus far being $3500.

A scheme to classify all matter has been designed, a task that required 1 year and 2 months. The scheme was taken out to experts in the field to be broken down if possible. It stood up. Since the information is vast, a system of coding had to be devised for its mechanization. This also was accomplished in the first year and a half of the center's operation.

During this year and a half, the center has also been able to collect information and conduct research. Some 21,000 items of information have been collected and processed. This has all been accomplished on an operating budget of only $75,000 per year. The center now plans to raise its operating budget to $225,000 a year, increase its personnel, and undertake to serve the total needs of industry, the colleges, the Army, Navy, and Air Force for information on all thermophysical properties of matter.

The center proposes to issue each year a 1000-page *Bibliography on Thermophysical Properties,* the first volume to appear about 1 January 1959. The center also proposes to publish "Most Probable Values of Properties," a set of tables. Touloukian sees the center's responsibility as about equally divided between mechanized search of the literature and the supervision of new experimental research.

Hearings on Soil and Water Research Facilities

The U.S. Department of Agriculture has announced the locations and dates of public hearings to be held in connection with a study of needs for soil and water conservation research facilities. The study is being made at the request of the Senate Committee on Agricultural Appropriations.

Hearings have been scheduled as follows: 14 October, Rapid City, S.D.; 15 October, Salt Lake City, Utah; 16 October, Boise, Idaho; 24 October, Charleston, S.C.; 28 October, Sacramento, Calif.; 30 October, Phoenix, Ariz.; 31 October, Amarillo, Tex.; 6 November, Harrisburg, Pa.; 7 November, Boston, Mass.; 14 November, Washington, D.C.; 17 November, Des Moines, Iowa; 18 November, Fort Wayne, Ind.; 19 November, Nashville, Tenn.; 20 November, New Orleans, La.

Farmers, ranchers, farm organizations, and lay groups interested in soil and water research are invited to present their recommendations at the hearings. Formal channels have been established for federal agencies, state agricultural experiment stations, and state extension services to submit their recommendations direct to the working group. Members of the group are: G. M. Browning of Iowa State College, Ames, representing the state agricultural experiment stations; Gerald E. Ryerson of the Soil Conservation Service, Washington, D.C.; and Cecil H. Wadleigh and Darnell M. Whitt of the Agricultural Research Service, Beltsville, Md.

When the working group was appointed on 29 July, it was directed to focus its attention on problems of national and regional importance, leaving for the attention of the states problems having only state or local significance. The group will consider research needs in watershed engineering, erosion control, water management, soil management, and basic soil problems.

News Briefs

The Atomic Energy Commisison has announced that it proposes to license two New England firms to collect low-level radioactive wastes and to dispose of them at sea. The licenses would be in effect through 31 August 1960. The Walker Trucking Company of New Britain, Conn., will be licensed to dispose of waste byproduct material (radioisotopes) and waste source material (uranium and thorium). The New England Tank Cleaning Company of Cambridge, Mass., will be licensed to dispose of byproduct material (radioisotopes). Each firm will be authorized to collect pre-packaged and labeled waste materials and to dispose of the materials in the Atlantic Ocean in containers made heavy enough to insure sinking to at least 1000 fathoms.

* * *

Clifford F. Rassweiler said recently in his presidential address to the American Chemical Society that the nation needs a fourth military service devoted entirely to research and development. He said the new force ought to be made equal in stature to the Army, Navy, and Air Force and should have its own representatives on the Joint Chiefs of Staff.

* * *

Metropolitan Life Insurance Company statisticians, who have been charting the poliomyelitis experience of the company's industrial policyholders, report that not a single death from the disease occurred in the insured group during the first 6 months of the year, but that there were three deaths in July. Only 2220 cases of poliomyelitis were reported for the whole population of the country in the 35 weeks ending 30

August. This is nearly three-fifths of the total for the like period of 1957 and slightly less than one-seventh of the annual average for the corresponding period of 1953–56. The only adverse development so far this year is the excess in the number of paralytic over nonparalytic cases, a reversal of the situation in 1957.

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The Japanese Government proclaimed the national adoption of the metric system a year ago. After a 3-month grace period beginning 1 October, commercial companies and others using the old measures will be liable to fines of up to 50,000 yen ($138.89).

* * *

The Atomic Energy Commission has invited United States architect–engineering firms to submit proposals for studies on a heavy water moderated power reactor capable of operating on natural uranium fuel. The design studies, to be made on a cost-plus-fixed-fee basis, will supplement developmental work already in progress. Proposals must be received by the commission by 29 September 1958 and may be submitted by an individual organization or by groups of organizations. For information, write to: Director of Reactor Development, U.S. Atomic Energy Commission, Washington 25, D.C.

* * *

The centennial of the publication of Rudolph Virchow's *Cellular Pathology* is being celebrated throughout 1958 by the Armed Forces Institute of Pathology, Washington, D.C. The celebration program, which started in March with the first of a series of public lectures, is being concluded with five more lectures. The first will be delivered on 15 October by R. D. Lillie of the National Institute for Arthritis and Metabolic Diseases, and the last is scheduled for 17 December, when K. M. Brinkhous of the University of North Carolina School of Medicine will speak.

Grants, Fellowships and Awards

Arctic. The Arctic Institute of North America is offering field research support in 1959 for scientific investigations dealing with the arctic and subarctic regions of North America. Applications are invited by those who have demonstrated their ability to conduct research work of superior quality in some field of science. Proposals will be considered in any field of arctic scientific research, but those in fields in which scientific knowledge is lacking are especially desired. Priority will be given to field investigations.

Facilities of the Arctic Research Laboratory at Barrow, Alaska, are available for a limited number of scientists for both summer and winter investigations. The facilities include both housing and equipment. Arrangements may be made at other places.

Application forms may be obtained from the Arctic Institute of North America, 3485 University St., Montreal 2, P.Q., Canada, or 1530 P St., NW, Washington 5, D.C. Completed applications should be received *before 15 October.*

Fertility. The Lalor Foundation has announced the program of awards for 1959 which it is offering to college and university faculty members for research in the biological sciences. These awards are to be for support of research on the fundamental biochemical and biophysical mechanisms concerned with fertility and reproduction in various forms of life. The objectives are to work for more complete understanding of the basic phenomena involved and ultimately toward better possibilities for biological regulation and control.

Grants may range up to $8000 per year and will be scaled in proportion to the scope and duration of the projects approved. Preference will be given to younger members of university and college staffs with an upper age limit of 45 years. The work may be carried out at the applicant's own institution or elsewhere.

The foundation will also grant postdoctoral summer or short-term research awards in the field described on projects which, for example, would be appropriate to the Marine Biological Laboratory at Woods Hole, Mass., or elsewhere. For these awards, the stipends will normally not exceed $900 for a single man or a woman, $1100 for a married man working at his home institution, and $1250 for a married man with principal program at another institution.

Applications and inquiries should be directed to the Lalor Foundation, 4400 Lancaster Pike, Wilmington 5, Del. The deadline date for receipt of applications is *15 January 1959.*

General. The deadline for applications for National Science Foundation senior postdoctoral and science faculty fellowships is *15 October.* Inasmuch as this is the first year during which these awards will be made annually rather than biannually, applications for awards for 1959 must be submitted by the October closing date. Application materials may be obtained from the Division of Scientific Personnel and Education, National Science Foundation, Washington 25, D.C.

Awards will be made in the mathematical, physical, and engineering sciences; medical and biological sciences, including anthropology and psychology (excluding clinical); and in selected social science fields. Included as well are interdisciplinary fields which overlap two or more scientific disciplines.

Candidates for senior postdoctoral fellowships must be United States citizens who have held the doctoral degree for a minimum of 5 years or have equivalent education and experience. Under arrangements made by the National Academy of Sciences, candidates' qualifications will be evaluated by carefully chosen panels of scientists. Final selection of approximately 100 fellows will be made by the National Science Foundation.

The science faculty fellowships are directed toward college teachers of science who wish to improve their competence as teachers. These fellowships are open to application by any United States citizen who holds a baccalaureate degree or its equivalent, has ability and special aptitude for science teaching and advanced training, and has taught at the collegiate level as a full-time faculty member for a minimum of 3 years and intends to continue teaching. Under arrangements made by the Association of American Colleges, applicants' qualifications will be evaluated by persons especially competent to make judgments about the demonstrated and potential ability of the applicant as a teacher of science. Final selection of approximately 300 fellows will be made by the National Science Foundation.

Scientists in the News

CARL FRIEDRICH FREIHERR VON WEIZSACKER, German physicist and philosopher, has received the Goethe Prize, high honor bestowed every 3 years by the city of Frankfurt, Germany. In recent years Weizsäcker has come to public attention because of his writings on life in the atomic age. In a series of articles entitled *Leben mit der Atombombe* he has analyzed basic problems of our day from the viewpoints of both the philosopher and the physicist. As he was awarded the Goethe Prize, Weizsäcker was lauded for helping to bridge the gulf between the natural sciences and the liberal arts.

CHARLES M. SPOFFORD, bridge designer and professor emeritus at Massachusetts Institute of Technology, will receive the Frank P. Brown Medal of the Franklin Institute on 15 October. He is being honored for: "The engineering, aesthetic and educational accomplishments of his life work, exemplified in his prompt recognition, espousal and clarification of valid structural theories; his design of many large and beautiful bridges, and other prominent engineering works; his contributions to en-

gineering education through teaching and administration of an engineering educational department; and his authorship of widely used textbooks."

JOHN J. LANDER, director of electrochemical research at the Delco–Remy Division of the General Motors Corporation, is the first recipient of the Research Award of the Battery Division of the Electrochemical Society. He is being honored for his pioneering work on the kinetics of the anodic corrosion of lead and specifically for his paper in the June 1951 issue of the society's journal entitled "Anodic Corrosion of Lead in Sulfuric Acid Solutions." The award will be presented at the Battery Division's luncheon to be held during the society meeting in Ottawa, 28 September–2 October.

Major General HARRY G. ARMSTRONG, U.S. Air Force (MC), a pioneer in aviation and space medicine and former Surgeon General of the Air Force, has retired after almost 30 years of military service. In 1949, while he was commandant of the U.S. Air Force School of Aviation Medicine, Armstrong established the department of space medicine, the first laboratory of its kind.

ALBERT ROSE, senior member of the technical staff, RCA Laboratories, Princeton, N.J., has been named recipient of this year's David Sarnoff Gold Medal Award by the Society of Motion Picture and Television Engineers. The award is being given to Rose for "basic contribution to the development of the Orthicon, Image Orthicon and Vidicon television pick-up tubes."

A. E. RHEINECK, research chemist and research supervisor for the Archer – Daniels – Midland Company, Minneapolis, Minn., has been appointed professor of chemistry in the School of Chemical Technology at North Dakota State College, where he will teach and conduct research in the area of protective coatings.

RHODA STASIAK, who formerly was in charge of the infrared spectroscopy laboratory of the American Viscose Corporation, has been appointed research associate in the analytical and physical chemistry division of the Squibb Institute for Medical Research at New Brunswick, N.J.

LOUIS A. TURNER, director of the physics division at Argonne National Laboratory, has been named deputy director of the laboratory. Turner will fill a position which has been vacant since Norman Hilberry, formerly deputy director, became director at Argonne in 1957.

THOMAS H. BREM has been promoted to the chairmanship of the department of medicine at the University of Southern California School of Medicine. The announcement follows the retirement of PAUL STARR, head of the department from 1948 to 1955 and co-head since then. Brem and Starr have shared the chairmanship for the past 3 years, Brem being in charge of teaching and Starr in charge of research. Henceforth, Brem will be responsible for both fields.

The Foundation for Integrated Education, 246 E. 46 St., New York 17, is sponsoring a tour of this country by C. GATTEGNO, secretary of the International Commission for the Study and Improvement of the Teaching of Mathematics, a growing group drawn from principal European and British universities and teacher's organizations. Gattegno is co-developer of Cuisenaire–Gattegno teaching aids, materials and methods that were introduced on this continent last year—systematically in Canada, and in scattered centers in the United States. They have been in use in Europe and Great Britain and other countries for periods varying from 6 to 25 years and are now employed in some 20 countries.

Gattegno is holding consultations with teachers and school administrators throughout the country. At present he is traveling in the states of Washington and Oregon. He will be in Washington, D.C., on 7 November.

ROGER H. HILDEBRAND, associate professor of physics at the University of Chicago's Enrico Fermi Institute for Nuclear Studies, has been appointed associate laboratory director for high energy physics at Argonne National Laboratory.

Recent Deaths

ASA C. CHANDLER, Houston, Tex.; 67; internationally known specialist in tropical medicine and parasitology; retired in 1956 as chairman of the department of biology at Rice Institute; taught at Oregon State College from 1914 to 1918; headed a research laboratory at the British School of Tropical Medicine in Calcutta from 1923 to 1927; author of textbooks; 23 Aug.

CHARLES E. DECKER, Norman, Okla.; 89; research professor emeritus of paleontology of the University of Oklahoma School of Geology since 1944, had been a member of the faculty of the School of Geology since 1916; 23 Aug.

NATHAN C. FOOT, Bronxville, N.Y.; 77; professor emeritus of surgical pathology of Cornell University Medical College; professor of pathology at the University of Cincinnati College of Medicine from 1928 to 1932; member of the pathology staff at Harvard Medical School from 1912 to 1922; 5 Sept.

MAX GROTEWAHL, Kiel, Germany; 63; Arctic explorer who led several expeditions; founder and director of the Kiel Archive for Polar Research, one of the four major Arctic study centers in the world; member of the Arctic Institute of North America and adviser of the American Polar Society in Washington; 7 Sept.

PASQUALE MARINA, Kearney, N.J.; 72; inventor and self-educated mathematician; invented a special carpenter's rule and a new logarithm table; 4 Sept.

LOUIS MONTGOMERY, Forest Hills, N.Y.; 62; psychoanalyst who studied with the late Sigmund Freud; former director of the Association of Applied and Clinical Psychoanalysis; 2 Sept.

RUDOLPH NORBERG, West Palm Beach, Fla.; 77; retired in 1949 as board chairman of the Electric Storage Battery Company of Philadelphia; co-developer of the Willard storage battery and of new types of batteries for cars, submarines, and airplanes; 6 Sept.

GILBERT J. PALEN, Philadelphia, Pa.; 88; professor emeritus of otology at Hahnemann Medical College; 6 Sept.

EDWARD HOLMAN RAYMOND, Litchfield, Conn.; 79; professor of oral pathology and bacteriology at Columbia University from 1920 to 1924; one of the first to use novocaine for local anesthesia in dentistry; 8 Sept.

GUSTAVE T. REICH, Philadelphia, Pa.; 67; chemical engineer; consulting manager and director of the Federal Yeast Corporation, Baltimore, Md.; specialist in alcohols; holder of 95 patents; 17 Aug.

ADOLPH STERN, New York, N.Y.; 79; psychoanalyst at the Medical Arts Center; president of the New York Psychoanalytic Institute; studied under Sigmund Freud in Vienna, Austria, in 1922; 22 Aug.

MICHAEL J. TAKOS, Miami, Fla.; 39; director of the research and special studies section of the Dade County Health Department; had taught biology at Emory University, Atlanta; 10 Sept.

NORRIS W. VAUX, Philadelphia, Pa.; 76; professor of obstetrics at Jefferson Medical College, 1931–46; former director of obstetrics at Pennsylvania Hospital; Pennsylvania secretary of health, 1947; 19 Aug.

GEORGE C. VEDOVA, Glen Ridge, N.J.; 64; chairman of the mathematics department of the Newark College of Engineering from 1947 to 1958; had taught at St. Johns College (Annapolis, Md.), the Virginia Polytechnic Institute, and Haverford College; 5 Sept.

Book Reviews

Aggression. John Paul Scott. University of Chicago Press, Chicago, 1958. xi + 149 pp. Illus. $3.75.

This compact little book provides a good over-all view of what we know, to date, about the biological aspects of mammalian aggression. Scott's many years of behavior research at the Roscoe B. Jackson Memorial Laboratory have given him a sure touch not only in describing the actions of animals but in recognizing the relevant antecedents of even such complex forms of behavior as aggression. Written for the series "The Scientist's Library—Biology and Medicine," this book is technical at the knowledge level of biological and behavioral scientists but reports broad conclusions rather than the interim puzzlements, excitements, or arguments of those who are presently immersed in such research. It is eminently readable—delightfully so in many places—and the author has not hesitated to introduce thoughtful commentary on the social implications of his biological facts. The University of Chicago Press is to be commended for establishing this popular (among scientists) series and congratulated for having got such a skillful recounter to present this—for biology—difficult area of behavioral science.

Scott defines aggression as the act of initiating a fighting attack. He describes the mechanics of the process by which animals learn to attack and to refrain from attacking and shows how the facts fit a starkly Pavlovian theoretical model. To psychologists, this will be the most interesting chapter in the book, for by avoiding the more customary definition of aggression (that given in terms of intent to injure), Scott has been able to conceptualize aggression as a simple operant act. If this procedure leaves something to be desired in the explanation of human aggression, it nonetheless orders well a significant body of observations on the lower mammals.

Successive chapters describe the physiology of aggressive behavior. The physiological chapter provides an updating of older theories (Cannon's emergency and the James-Lange self-perception), with a brief and not-too-technical description of recent research. Scott concludes that aggression must be understood as an externally instigated reaction, depending for its duration and vigor on a complex feedback mechanism. This rejection of an instinct theory that implies spontaneous internal instigation will doubtless satisfy biologically oriented psychologists; it still bypasses the question of how spontaneous attacks are instigated in the absence of primary stimulus conditions. While the Pavlovian model can probably be expanded to account for such behavior, Scott has made no effort to examine the complexities of human aggression that have led psychoanalytic investigators to posit instinctual sources of some of this behavior.

The book is at its best when it treats of the lower animals—their physiology and the effects of their environments. The casual disregard of extensive areas of research on human aggression, however, leaves the problem of aggression, as such, only half covered. The book points up the apparent dilemma of current comparative psychology over whether to limit consideration of a behavioral problem to its infrahuman manifestations—and thus maximize the importance of this research discipline—or to recognize man as an important object of comparative study—and perhaps make an inquirer wonder why we should *infer* answers to practical human problems from mice, rather than seek the answers by direct investigation of man himself. Scott has chosen to emphasize the lower mammals and has done a good job of it. However, since he has had to display, also, important *species* differences, even among breeds of dogs, one cannot but wonder how applicable his conclusions are for an understanding of human aggression. Perhaps this is to say no more than that Scott did what he set out to do so effectively that one only regrets he did not do twice as much.

ROBERT R. SEARS
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The Chemistry and Biology of Yeasts. A. H. Cook, Ed. Academic Press, New York, 1958. xii + 763 pp. Illus. $22.

In spite of the great progress that has been made in recent years on the whole frontier of yeast research, it is probably correct to say, as Winge and Roberts maintain in their excellent chapter, "Life history and cytology of yeasts," that of all organisms yet investigated, none have caused more disagreement among cytologists than yeasts. Although the action of yeast has been known and used by man since time immemorial and the yeast organism was observed by Leeuwenhoek as far back as 1680, we must admit that the deeper we penetrate into the secrets of this organism that plays such an important role in human life, the more we become aware of great areas of physiological and biochemical realities that need further elucidation.

Yeast research is presently a focal point of scientific activity, cutting across biophysics, biochemistry, ecology, cytology, genetics, technology, nutrition, physiology, and pathology; the subject can no longer be treated exhaustively and authoritatively by one single specialist but requires the cooperation of numerous scientists, each an expert in his area of research, for presentation of a comprehensive and systematic and yet not too unwieldy assessment of the present status of this very broad, and yet inadequately explored, field of knowledge, still in continuous flux.

The great and difficult task of coordinating numerous contributions from all frontiers of yeast research has been admirably accomplished by the editor, who is himself an eminent authority in yeast research. He has presented here the first comprehensive work to encompass in one volume a vast store of information on all aspects of yeast research.

While the book will be an invaluable reference work in the library of mycologists and biochemists, it should also become an efficient tool in the hands of nutritionists, plant and animal pathologists, and such professional people as bakers, brewers, distillers, and food technologists in general. However, it should also be read by advanced students of cytology, plant physiology, and genetics, whose well-established notions about living matter and life processes will be shaken in their foundations by many facts presented here that should become general knowledge in the field of life sciences. Space permits me to mention only a few outstanding items.

We like to accept it as a basic fact of life that germ cells have half the number of chromosomes of somatic cells. We also know that yeasts reproduce both sexually and asexually and exist in either haploid or diploid phases. However, in contrast to generally accepted laws of reproduction, vegetative growth of yeast can take place in the haploid and diploid phase as well as in a mixture of both, and what formerly were thought to be two distinct genera are actually only two phases of one and the same genus.

Yeasts have definite sexuality, and whether or not sexual reproduction takes

place depends on the presence of cultures of opposite mating type and the action of a chemical substance which induces copulating processes. This substance acts at a distance, and the result of this action could be observed even in a solid nutrient medium between separated colonies of yeast cells of opposite mating type.

No less fascinating than the chapter on cytology is that on "Yeast genetics," written by the same authors. The rapid vegetative growth of yeast in cultures and the possibility of isolating single cells or spores with the help of micromanipulators and of carrying out artificial hybridization experiments offer the geneticist many advantages he cannot find in other organisms. Thus it is understandable that, from a genetic point of view, yeast is one of the most thoroughly investigated of microorganisms. We know a large number of individual genes of which those inducing chemical specificity of action are of great theoretical and practical importance; on the basis of linkage of these genes, chromosome maps have been constructed; and the existence of inbreeding degeneration, hybrid vigor, and mutations have been demonstrated. But the most interesting and presently most active field of research is that of cytoplasmic inheritance, whose far-reaching implications in biological theory and even in medicine, especially in cancer research, have not yet been fully realized.

The "Aspects of chemical composition of yeasts" are expertly covered by A. A. Eddy, while "Yeast growth" is ably dealt with by E. O. Morris from both the chemical and physiological point of view. Until recently it has been a common assumption that yeasts are unable to assimilate atmospheric nitrogen, but now we have conclusive evidence that certain strains of *Rhodotorula* and at least one strain of *Saccharomyces,* when grown in a nitrogen-free medium but in an atmosphere containing isotopic nitrogen, are able to convert the latter into organic compounds of their cell substance. However, if these facts are considered only as of "mainly academic interest," as the author indicates, a vigorous objection seems to be in order. In a world so short of protein and with yeast promising to play an ever-increasing part in protein supply for human beings and animals, the fact that certain yeast strains should be able to "fix" nitrogen from the air appears to be not only of great theoretical but of even greater practical significance. There is no reason why scientists should not be able to discover, or by way of induced mutations be able to "breed," organisms that will have a much greater nitrogen-fixing ability than those presently under consideration.

Very readable and illuminating are the contributions on "Fermentation and respiration," by F. F. Nord and S. Weiss; on "Synthesis and degradation of carbohydrates," by W. E. Trevelyan; on "Nitrogen metabolism," by G. Harris; on "Yeast technology," by Magnus Pyke; on "Pathogenic yeasts," by C. G. Ainsworth; on "Food spoilage," by M. Ingram; and on "Flocculation," by H. E. Jansen.

In summarizing I must say that this work, to which scientists from England, Holland, Denmark, and the United States have made such eminent contributions, is a model of international scientific cooperation and, thanks to the painstaking efforts of its editor, also of conciseness and unity of presentation. In both text and appearance it does honor to the publisher; it should be recommended as a first-class scientific standard work to all who take a practical and theoretical interest in the agent of man's oldest industry—fermentation.

FRANCIS JOSEPH WEISS
Arlington, Virginia

The Effects of Atomic Radiation on Oceanography and Fisheries. Report of the Committee on Effects of Atomic Radiation on Oceanography and Fisheries of the National Academy of Sciences, Study of the Biological Effects of Atomic Radiation. Publication No. 551. National Academy of Sciences–National Research Council, Washington, D.C., 1957. vii + 137 pp. $2.

The material presented in this volume is much wider in scope and interest than the title suggests. This comment should not be taken as meaning that the members of the Academy committee have evaded the issue presented to them. The issue of the biological effects of radiation is one that confronts all persons and governments, and the seeming absence of authoritative information makes for the prevalence of contradictory opinions. While the gaps in knowledge are freely indicated in this report, the careful collation of relevant information enables the reader to learn that considerable and careful attention has been given to the problems which the use of atomic phenomena raises.

In addition to an introduction on the importance of the ocean as a receptacle for radioactive materials, there are 13 chapters, dealing with properties of atomic wastes, natural radiations received by organisms, disposal and dispersal of radioactive elements, effects of ecological relationships on transport and dispersal, effects of radiation on aquatic organisms, and isotopic techniques in chemical and physical oceanography. Although each chapter is self-contained, there is extremely little repetition, and the freshness in approach provides much stimulus to scientific thought. Despite the bias of the title towards the effects of atomic radiation, many fundamental fisheries and oceanographical problems are brought forward and receive illuminating attention.

The most serious type of hazard likely to arise from the addition of radioactive wastes to the sea is that following the concentration of wastes by organisms used as human food. The increasing use of the sea as a source of food for the rapidly expanding world population enhances the value of knowledge on this matter. As both the qualitative and quantitative natures of food chains differ in the various parts of the world, local studies are necessary. The information arising from such studies is indispensable to programs of proper fisheries management, and this interrelationship once more emphasizes the importance to fisheries science of a close synthesis with oceanographical knowledge. Similarly, the problems of radioactive disposal demand from oceanography a knowledge of currents, wind effects, sedimentation processes, and so forth—all matters of theoretical and applied importance in their own right but matters which ask for more urgent attention in the stress of the present age.

These questions and many others are critically considered throughout the report, and ingenious methods are suggested for their study. The collection of these stimulating and authoritative articles together in one volume is especially to be commended, as such reports are often buried in special publications issued in temporary form. It is hoped that the statement in the foreword that the study is a continuing one means that further volumes will appear.

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Colorimetric Determination of Nonmetals. David F. Boltz, Ed. Interscience, New York, 1958. xii + 372 pp. Illus. $8.50.

This book is volume VIII of a series of monographs on chemical analysis. As such, it complements volume III, Sandell's *Colorimetric Determination of Traces of Metals.*

Under the editorship of David F. Boltz, 14 authors, including Boltz, have cooperated in writing the 11 chapters. The first of these chapters covers briefly the principles and practices of colorimetric and related photometric methods. The other ten cover methods believed to

be most suitable for the following elements (or certain of their compounds): phosphorus, silicon, nitrogen, chlorine, bromine, iodine, fluorine, sulfur, tellurium and selenium, and boron. In general, following an introduction, each chapter covers separation, methods of determination, and important specific applications.

The list of supporting literature cited includes 718 references. A chemist informed about the literature would note that only two of the references cited appeared as late as 1957 and only six in 1956, although the book did not appear until well into 1958. The following are possible explanations for this small number of late citations: (i) there has been no more recent work; (ii) if there has been, the methods have not been sufficiently tested to justify inclusion in the volume; and (iii) the inevitable time lag in publication prevented inclusion of late work. In evaluating the up-to-dateness, of course, an experienced worker will rely on the date of the latest references cited rather than on the date of the copyright.

Three notable nonmetals not included are carbon, hydrogen, and oxygen. I would have welcomed chapters on these important elements, especially on hydrogen ions and simple inorganic compounds such as water, carbon monoxide, and carbon dioxide. Obviously, the wealth of organic compounds susceptible to colorimetric measurement could not be included.

This book is a valuable reference compilation for the elements covered and no doubt will be often cited, as Sandell's companion volume has been. The methods are carefully selected and concisely stated. Meticulous editing and proofreading have reduced inconsistencies and typographical errors to a minimum.

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Purdue University

Handbuch der Physik. vol. XXXIV, *Corpuscles and Radiation in Matter, II*. S. Flügge, Ed. Springer, Berlin, 1958. viii + 316 pp. Dm. 78.

This new volume of the *Handbuch der Physik* contains six more or less independent articles pertaining to the processes involved in the slowing down and disappearance of particles and radiation in matter. The emphasis throughout is on the experimental results; theory is introduced only in order to show the agreement between theory and experiment.

The first article, written by R. Kollath, is in two parts—the first on slow electrons and the second on slow ions. The discussion of electrons starts with a careful review of the experimental determinations, both as to methods and as to results. The comparison with theory that follows is restricted to angular distributions, these being the most sensitive to test. The part concerning the passage of slow ions through gases starts with a discussion of sources and proceeds to the experiments. The results are indicated in some detail, with major emphasis on the role of exchange and resonances. A short paragraph about negatively and multiply charged ions concludes the article.

The second article, written by R. D. Birkhoff, treats the passage of fast electrons through matter. Summaries of the theories for various types of events are given and compared with the results of experiment. Free electron-electron and positron-electron collisions are discussed. This is followed by a section on stopping power for electrons, including density effect and Cerenkov radiation. Considerable space is given to a treatment of collisions with the conduction plasma. The rest of the article treats the statistical behavior of electrons. Energy loss and straggling are well treated. This is followed by a thorough discussion of the theory and results in multiple scattering. The results of single nuclear scattering calculations by several authors are collected in convenient form. Finally, the effects of thick targets and associated range relations are presented.

Positronium is the subject of the third article, written by L. Simons. The theoretical results are presented in the first part. There follows a more or less historical discussion of the experiments on positronium, including quenching, spectra, angular correlations, and solid state aspects, which does very well in introducing the reader to all but the most recent work.

The fourth article, written by E. Merzbacher and H. W. Lewis, is on x-ray production and ionization by heavy ions. It starts with a theoretical discussion of some length. Experimental results are given and compared to the theory, particularly with respect to ionization. The article concludes with a short section on continuous radiation.

Energy loss by heavy particles in the energy range below 10 Mev is treated by W. Whaling in the fifth article. The results in this region are mostly experimental. A very useful collection of results has been assembled. Most of the values given are for protons and alpha particles, but a few results for heavier ions are included. I regret that the article does not include results at higher energies, which occupy a position of major interest today.

In the final article, R. D. Evans gives a comprehensive treatment of the Compton effect. Starting with a historical background, he discusses the early experiments and their later improved versions. The treatment is such as to point up the similarities and differences of the classical and quantum treatments. Formulas, graphs, and tables for various cross sections are given, including some energy distributions useful in instrumentation. Following this is a summary of absorption data for photons. The effect of electron binding on the photon scattering is discussed, including Rayleigh scattering. Finally, there is a section on Compton scattering by magnetically oriented electrons, with an indication of the possibility for detecting circular polarization.

Two general items disturbed me slightly. The termination date of the bibliographies was not always clear, and some of the graphs appear to be only of qualitative value. The articles do, however, supply good introductions to the various topics.

Walter Aron
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University of Virginia

Anatomist at Large. An autobiography and selected essays. George W. Corner. Basic Books, New York, 1958. v + 215 pp. $4.

George Corner presents a brief but poignant glimpse of his personal and professional life as introduction to ten selected essays and addresses from his pen. The autobiographical matter tells of family, and of boyhood and education in Baltimore. It tells of the young doctor's decision to follow a laboratory career and of the felicitous associations and circumstances accompanying a productive life as a distinguished leader in investigations of the sex hormones. One could wish for more than 64 pages of autobiography in this book of 215 pages. Readers would have welcomed inclusion of a photograph of the author.

Arranged in chronological sequence, from student days to retirement, the several essays and addresses suggest a measure of the wisdom and humanity of the author. Three essays, reflecting his scholarly interest in medical history, are followed by a look at the scientist in his workshop. In this account of his "quest for a hormone" one may discern the undercurrent of subdued excitement, the sense of urgency, and the aura of imminent discovery that pervaded his laboratory. Such an atmosphere is heady wine, and it drew able and dedicated investigators to his side from across the world.

The addresses offer sage advice and reflective comment on subjects ranging from the attributes of a good physician to a contemplation of the "incomprehensibles" that the thoughtful scientist cannot evade. Finally, there is consideration

of the duty of the scientist as a leader in education, and of trends in this area.

This is a very readable account of a full and satisfying career. It was a fitting compliment that Corner's official retirement as director of the department of embryology of the Carnegie Institution of Washington, in December 1955, was followed immediately by his appointment as historian of the Rockefeller Institute for Medical Research.

ELBERT B. RUTH
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Atmospheric Explorations. Papers of the Benjamin Franklin Memorial Symposium of the American Academy of Arts and Sciences. Henry G. Houghton, Ed. Technology Press of Massachusetts Institute of Technology and Wiley, New York; Chapman & Hall, London, 1958. x + 125 pp. Illus. $6.50.

The five scientists represented in this small book on atmospheric electricity and the upper atmosphere are active along the "cutting edge" of atmospheric research. They know their subjects, and they believe that they have something worth while to say. These qualities insure a good technical book.

Henry Houghton of Massachusetts Institute of Technology has edited papers presented at the Benjamin Franklin Memorial Symposium of the American Academy of Arts and Sciences, in 1956, by Ross Gunn of the U.S. Weather Bureau, Joachim P. Kuettner of the Geophysical Research Directorate, Leonard B. Loeb of the University of California, Harry Wexler of the U.S. Weather Bureau, and Henry G. Booker of Cornell University.

Gunn reports that the charge distribution on cloud droplets and on rain is to be explained by diffusion of atmospheric ions, and he presents the relevant quantitative theory; he brings a simple and rational order to a problem which has often been discussed in a complex and confusing manner. Kuettner discusses some aspects of the problem of charge segregation in thunderstorms and presents his quantitative ideas about the crucial processes; this important problem still appears to be characterized by interesting and puzzling data unsupported by a solid theoretical structure. Loeb, to whom chief credit is due for the explanation of the mechanism of lightning, here gives further evidence of the similarity between lightning and the electric spark. Wexler presents some of his current thinking on large-scale upper-atmosphere local temperature changes (he attributes them to adiabatic changes accompanying large-scale cyclonic systems) and the question of upward or downward propagation of large-scale disturbances (he favors upward propagation but recognizes that downward propagation is conceivable). Booker describes nine phenomena associated with the scattering of radio waves by the ionosphere which are not easily explained. He suggests that atmospheric turbulence in the ionosphere may provide the key to their explanation but recognizes that no quantitative theory exists.

The scientific study of the atmosphere presents a number of trying difficulties; not the least of these is the fact that, whereas activity in recent years has been rather great, progress has been disproportionately small. The result has been that the good work tends to get lost in the abundance of indifferent work. Some of the most important problems today appear to be enmeshed in tangled chains of suppositions and in endless data which are never quite complete or quite accurate enough. It is in facing this situation and in trying to overcome it in a limited field that *Atmospheric Explorations* has made its most important contribution. Other books with similar objectives by equally eminent and capable scientists are needed to clarify and unify other of the most important atmospheric problems.

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Admission Requirements of American Medical Colleges, Including Canada, 1958–59. Compiled by Helen Hofer Gee and E. Shepley Nourse. Association of American Medical Colleges, Evanston, 1958. viii + 227 pp. $2.

This new edition of *Admission Requirements of American Medical Colleges* contains the latest official information on premedical preparation in general and the requirements of each medical school in the United States and Canada.

Students seeking vocational guidance will find useful information on the specific requirements and costs for each school.

New Books

Advances in Enzymology and Related Subjects. vol. XX. F. F. Nord, Ed. Interscience, New York, 1958. 495 pp. $12.50.

The Birds. Oskar Heinroth and Katharina Heinroth. Translated by Michael Cullen. University of Michigan Press, Ann Arbor, 1958 (published as *Aus Dem Leben Der Vogel,* Springer, Berlin, ed. 2, 1955). 181 pp. $5.

A Century of Darwin. S. A. Barnett. Harvard Univ. Press, Cambridge, Mass., 1958. 392 pp. $5.75.

The Changing Face of New England. Betty Flanders Thomson. Macmillan, New York, 1958. 197 pp. $3.75.

Ebb and Flow. The tides of earth, air, and water. Albert Defant. Translated by A. J. Pomerans. University of Michigan Press, Ann Arbor, 1958 (published as *Ebbe und Flut des Meeres der Atmosphäre und der Erdfeste,* Springer, Berlin, 1953). 121 pp. $4.

Elementary Statistical Physics. C. Kittel. Wiley, New York; Chapman & Hall, London, 1958. 238 pp. $8.

The Exploration of Time. R. N. C. Bowen. Philosophical Library, New York, 1958. 150 pp. $6.

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Reports

Evidence for a Double Peripheral Pathway for Pain

In a recent note (*1*) Jones reached the conclusion, after certain experimental procedures for pain stimulation, that "the best evidence of all varieties points to double pain as an artifact." She also indicated that she equates C-fiber pain with the second pain she could not demonstrate: "it seems difficult to believe that if there is a second, slower pain system leading to sensation, it would not appear. . . ." Since the author apparently misinterpreted our results (*2*) and also failed to note the significant point of the technique we employed, we take this occasion to amend her report.

When a peripheral skin nerve is stimulated electrically either percutaneously or with an inserted electrode, the threshold response perceived is one of a tapping touch sensation projected in the distribution of the nerve stimulated. This sensation remains unchanged regardless of frequency of stimulation until the intensity is increased 3 to 5 times. At this point a pricking pain sensation is produced by each shock, and the repetitive nature of the stimulus is perceptible at rates up to 30 per second (*3*). Comparable experiments in animals where the nerve action potentials were recorded, and some experiments in man where the nerve was removed for action potential recording, have shown that the pain sensation correlates with the delta spike of the nerve action potential. Collins (*4*) has confirmed these findings by recording the nerve action potentials *in situ* in man. Moreover, differential procaine anesthesia blocks pain and the small myelinated fibers, sparing touch and the large fibers (*5*). Thus fast pain is conducted by the small myelinated (delta) fibers of the A group.

When the limb is compressed by a blood pressure cuff inflated to a pressure of 250 mm-Hg for 35 to 45 minutes, *all* touch and pricking pain resulting from the stimulation of the distal skin surface is abolished. A deep aching pain which is delayed and exaggerated compared with the normal extremity can still be elicited by strong electrical stimulation of skin or by firm pressure; delayed warmth and cold may also be produced by appropriate stimuli. Electrical stimulation of a nerve trunk peripheral to the block, at a strength far above that previously required to induce touch and pricking pain, causes an obviously delayed excruciating burning pain which fuses and summates at a rate of three to five per second. This sensation is quite different in character from any sensation resulting from stimulation in the normal skin or nerve at weaker strengths before block. It is similar to the sensation derived from electrically or mechanically stimulated periosteum, as in a bruised shin. Where such pain is due to inflammation, it can be differentially blocked by procaine when pricking (delta) pain is intact (*2*). Correlated experiments in animals where the nerve action potentials were recorded have shown the behavioral response of pain when all but C-fiber afferents were blocked by pressure or electrical tetani (*6*). Thus slow pain is conducted by unmyelinated C-fibers.

Two volleys of subjective pain from single-shock electrical stimulation of an unblocked peripheral nerve have not been reported. The strength of electrical shock necessary to activate C fibers is many fold supramaximal for the delta fibers in the nerve and produces repetitive action potential responses. Such intense stimulation has made introspective observations impossible for us. In any case Jones did not stimulate peripheral nerves, and it is not certain what she stimulated in the skin when she did not obtain double pain from electrical stimulation.

We too reported that a biphasic subjective response to transient pain stimuli is often absent in normal subjects without nerve block. Our experiments with block show that two pain pathways exist, however seldom both can be identified introspectively when activated simultaneously under normal conditions. Each of these pains can be induced separately; they are qualitatively different and have quantitatively different latencies.

Jones' statement that we obtained "somewhat similar results" (to hers) following immediately the categorical statement, "Double pain was not found with normal subjects under controlled conditions," seems to indict either our experiments or our normality, besides being incorrect. As to her further statement that "the argument that a second pain system is suppressed by the faster system lacks evidence," we can only invite her to repeat the experiment with block and thus differentiate between argument and experiment.

We have previously pointed out (*2*) that the assignment of sensory experience to the results of stimulation of particular nerve fibers in experiments with a differential block are valid when an absolute end point of the absence of one experience or another is used. Arbitrary end points (*7*) must correlate with incomplete block of populations of nerve fibers; thus the conditions of experiment necessarily obscure the correlation of loss of sensation with loss of a fiber group, since the sensory end point by definition occurs before all the nerve fibers in any group in question are blocked. The fact that anatomical techniques have been inadequate to disclose structural differences in nerve endings which correlate with modalities of sensation cannot disprove the physiological observations related to nerve fiber diameters, thresholds, and conduction rates.

Recently Douglas and Ritchie (*8*) have shown that, in the cat, tactile stimulation produces afferent impulses in a faster subgroup of C fibers. If species differences are excluded from consideration, then the fact that no tactile sensation persists after block of myelinated fibers in man must indicate either that fast C fibers are blocked along with delta fibers or that *the perception of pain requires activation of a critical amount of C-fiber afferent activity*. In our experiments the cat saphenous C potential has been unchanged after compression block of A fibers; it would obviously be useful to know how pressure block affects Douglas and Ritchie's preparation.

While dealing with the functions of C fibers, we wish to add a statement that one of us was incorrect in implying that itch is a specific sequel to weak stimulation of delta fibers (*9*). Concurring with others (*10*) who have reported that C fibers are partly or entirely responsible for itch, we have found that the action of cowhage (itch powder) at the wrist persists after tourniquet block (35 to 40

Instructions for preparing reports. Begin the report with an abstract of from 45 to 55 words. The abstract should *not* repeat phrases employed in the title. It should work with the title to give the reader a summary of the results presented in the report proper. (Since this requirement has only recently gone into effect, not all reports that are now being published as yet observe it.)

Type manuscripts double-spaced and submit one ribbon copy and one carbon copy.

Limit the report proper to the equivalent of 1200 words. This space includes that occupied by illustrative material as well as by the references and notes.

Limit illustrative material to *one* 2-column figure (that is, a figure whose width equals two columns of text) or to *one* 2-column table or to *two* 1-column illustrations, which may consist of two figures or two tables or one of each.

For further details see "Suggestions to Contributors" [*Science* 125, 16 (1957)].

minutes) of all touch and pricking pain. It was noted that itch can be relieved by scratching even when the scratching itself cannot be felt. In one tabetic patient who lacks pricking pain and has exaggerated delayed pain, cowhage produced itch also. Using Shelley and Arthur's technique of implanting a small stimulating wire in the subepithelial layer of the skin, we find in the normal state a pricking itch, which becomes a most exquisite slowly summating "natural" itch after the block of large myelinated fibers. Shock intensity necessary to elicit itch increases up to several fold during pressure block.

Whether the itch of subepithelial C-fiber stimulation and the burning pain produced by C-fiber stimulation in nerve trunks relate to different numbers, groups, or patterns of pain fibers, or to different methods of stimulation is not determined. It still seems probable that a component of itch sensation is mediated by delta fibers as previously inferred.

In summary, we believe that it has been demonstrated that a second, long-latency pain is obtained after block of short-latency delta fiber pain. A similar sensation follows any painful stimulus in patients with tabes dorsalis who lack pricking pain, and the "protopathic pain" in the margin of denervated areas is of the same type. Differential blocks in these conditions, along with our own pressure block experiments, indicate that pain from C-fiber stimulation is enhanced by the absence of the myelinated delta pathway. We conclude that the failure of ourselves and others consistently to demonstrate two pains from one stimulus to the skin surface is due to the inadequacy of this experimental procedure as a differential method (*11*).

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Bishop and Landau obfuscate the several issues involved. The primary issue, and the one toward which my experimental investigation (*1*) was directed, is whether double pain sensations (awareness) from a single stimulus can be observed by a normal subject (the intact organism—neither tabetics nor amputees nor individuals with regenerating nerves, ischemic limbs, or nerve blocks) under properly controlled conditions of stimulation of cutaneous receptors, and at some psychophysically identifiable level of intensity. The reasons for concern with this issue are (i) descriptions of "double pain" as a normal sensory phenomenon are often encountered (*2*) and (ii) "double pain" is sometimes used as a measure of the effectiveness of a drug (*3*). In the first case, it is important for the scientific description and measurement of normal (nonpathological) sensation that the issue be clarified. In the second case, it is important in the evaluation of drugs that artifacts not be used as criteria of effectiveness.

The evidence points to double pain as an artifact of method when the normal organism (as defined above) is involved. Landau and Bishop, in spite of their present apparent disclaimer, did originally report (*4*) "somewhat similar results"—their experiment on eight normal, "unprejudiced" subjects, with heat, electrical, and brief mechanical stimuli showed that only three "thought" they could recognize a second pain response. I do not indict their experiment, for we are given no information on which to do so. But I do indict their inadequate report of it, and also the implication that their subjects were given the suggestion that there might be a second pain. Their present statement that "a biphasic subjective response to transient pain stimuli is often absent in normal subjects . . ." is the point I wished to emphasize. Without further information about stimulus control, instructions to the subject, or method, I cannot be sure whether the three subjects who "thought they could recognize" a second pain response were genuine positive cases or not. Since all the cases I have discovered—in normal subjects—can readily be explained by double stimulation, temporally or spatially, I must assume, evidence to the contrary lacking, that these can be so explained also. It is certain that hand-held needles and hot objects are totally unsuitable as stimuli for the investigation of this phenomenon. I am still of the opinion that the best evidence indicates that double pain as a normal sensory phenomenon is an artifact of method, for the reasons I originally set forth.

The second question, of the existence of a second pain system, demonstrable under abnormal physiological conditions, is quite distinct from the first and is inherently much more complex. Two of the basic issues are the following. (i) What are the facts and what are the assumptions. (ii) How far can one trust data obtained from pathologically functioning tissues in interpreting normal function.

The arguments for the existence of a second pain system stem most importantly from the various nerve-block and ischemia experiments [since the reaction-time evidence must be rejected as uncontrolled (*5*)]. I have already indicated (*5*) that I believe the nerve-block-ischemia data to be based upon pathological tissue conditions, and as such they must be interpreted with caution.

It is not easy to separate the facts from hypotheses or from experimental errors. I am willing to assume the following as facts:

1) After inflation of a sphygmomanometer cuff on a limb (which is partly pressure-block and partly ischemia, the balance of these and the nerve fibers affected varying with location and care in cuff application), reliable reports are obtained from human subjects that, after a period of time (variable), the sensory quality of pain evoked by noxious stimuli applied to receptors changes from a well-localized 'pricking' pain to a diffuse, burning or aching pain with greatly increased affect, even without intensity (subjective) change.

1A) Under the same conditions, the human subject reports a considerable delay in perception time.

2) In recording of nerve potentials from animal preparations, noxious stimuli evoke action potentials in small unmyelinated fibers called C-fibers.

2A) In the same situation, compression block of the nerve results in progressive disappearance of action potentials, in general the larger, myelinated fibers succumbing first, the small unmyelinated fibers surviving longer.

The connection between these two sets of data is hypothetical and is based on a number of assumptions, as well as on approximate temporal coincidence.

Qualitative argument. The assumption is that, since pain changes in quality after interference with normal physiological functioning, a new set of fibers is required. It is clear that touch, warmth, and cold also show similar qualitative changes (*6–8*). Furthermore, in other situations in which pain is poorly localized (as in visceral pain) and where the number of fibers subserving an area is reduced (as in partially denervated areas), a similar diffuse, burning or aching pain is present. I would assume the qualitative change to be due to a change in the temporospatial afferent pattern, following a reduction in number of active fibers, since there will, of course, be a distribution of survival times for the total population of the neurons in question.

Delay argument. The assumption is that, since perception of pain is delayed, a different set of neurons, with slower conduction times, is required. There is good evidence for a progressively increasing latency of action potentials in blocked nerves. Clark, Hughes, and Gasser (*9*) found slight slowing of conduction rates apparent within 15 minutes. Records of action potentials in the human ulnar nerve show progressive increase in latency after inflation of the pressure cuff (*10*). There was no discontinuity in the curve as would be expected if the composition of the group of active neurons had changed. Similar delays in perception occur in the other cutaneous senses also (*6, 7*). I would assume the perceptual delay to be due to the increasing latency of action potentials in neurons subjected to pathological conditions, and possibly also to synaptic delays occasioned by reduction in number of afferent impulses reaching the central nervous system.

Reliability of ischemia-nerve block data. The assumption is that such data are reliable and give reliable indices of conduction times of fibers. It is clear that the results of such experiments on human subjects are variable. If a large number of subjects is used and if the results are treated statistically (*6, 7*), the order of loss is seldom significant. Landau and Bishop themselves (*4*) found procaine blocks to be "inconclusive" because prick and deep pain disappeared together—that is, because the sensory results did not bear out the results of action-potential studies. Whereas touch may usually fail before pain in compression of a limb, the difference is not sufficiently dramatic to enable one to distinguish between small delta fibers and C fibers. There is evidence that the survival time of fibers under compression block is influenced by factors other than conduction rates. Frankenhauser (*11*), who dealt with touch fibers of different types, found that slowly adapting touch receptors in the rabbit were blocked later than hair touch fibers in spite of the fact that their conduction rates completely overlap those of the latter. He concluded that the fibers themselves have properties which are not predictable from observation of the impulses. In man, skin touch and hair touch also have different survival times (*12*), and in some areas hair touch survives pain (*6*).

There are some interesting results which suggest that the somatic sensory apparatus is much more complex than the current popular notions would have it. Between giving up all specificity, as Sinclair (*13*) does, and being bound to one or even two specific pain modalities, as Bishop and Landau are, one can conceive a rich patterning of general somatic sensation, with a large number of different sorts of receptors having different functions and different response characteristics. Maruhashi, Mizuguchi, and Tasaki (*14*) found a great variety of types of afferent nerve fibers in the toad and cat. These varied not only in fiber size, but in type of discharge (tonic or phasic), size of receptive field, and type of stimulus most effective. I would assume that a given stimulus excites more than one kind of fiber; thus the perceptual pattern is normally a complex one, not only spatially and temporally, but also in the balance of fiber types activated. And a different stimulus, since it affects a dynamic organism, will have a different effect.

My conclusions are as follows. (i) The exact function of the C-fibers is not known. These fibers respond to noxious stimuli but whether this results in awareness or merely feeds into either the reticular activating system or into an "affect" system is not certain. (ii) The peculiar quality and delay of pain sensations in nerve-block experiments are probably due to pathologically functioning tissues. (iii) Somatic sensation is a vastly complex system. (iv) Second pain is certainly an artifact in normal human experience.

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2 May 1958

Tolerance to Cereal Leaf Rusts

Resistance of crop varieties to plant rust fungi has been attained thus far mainly through utilization of the hypersensitive reaction wherein the host and parasite are mutually incompatible, resulting in localized necrosis of host tissue and in death or limited growth of the parasite. Such hypersensitivity, hereafter referred to as resistance, has afforded excellent initial rust protection to new resistant varieties produced by plant breeders. However, when such resistant cereal varieties have been extensively grown, new virulent varients (physiologic races) of the rust fungi have consistantly arisen to render these varieties fully susceptible in nature. Three genetically distinct hypersensitive types of resistance to the crown-rust fungus, *Puccinia coronata* Cda., have been transferred to extensively grown, commercial oat varieties in the United States. All such varieties, although providing high resistance to the initially occurring populations of the pathogen, have succumbed to attack by new physiologic races within a few years after they have been extensively grown. A similar fate has befallen oat and wheat varieties once resistant to prevalent races of stem rust, *Puccinia graminis* Pers. These experiences direct attention to the need for plant characters, other than resistance, whereby rust damage may be prevented or reduced.

Tolerance, enabling a susceptible plant to endure severe attack by a rust fungus without sustaining severe losses in yield or quality, is such a character. Caldwell *et al.* (*1*) have shown that the yield of Fulhard wheat in Indiana is not affected by severe attack of the leaf-rust fungus, *Puccinia recondita* Rob. ex. Desm. f. sp. *tritici.* This finding was supported by the report of Salmon and Laude (*2*) that the Fulhard variety was the highest yielding of 24 varieties studied over a period of years in Kansas, although it was one of the most severely attacked by leaf rust.

Evidence that a high level of tolerance to the crown-rust fungus, *P. coronata,* exists in the Benton variety of oats was obtained in studies at Lafayette, Indiana, from 1955 to 1957. Two pairs of oat varieties were involved in these studies, each pair being nearly "isogenic" except that one member of each pair was highly resistant to crown rust while the other was highly susceptible. Pair No. 1 consisted of the varieties Clinton 59 and Clintland. They differed essentially by a genetic factor for resistance to crown rust which had been introduced into Clintland by a cross of Clinton 59 × Landhafer, followed by three backcrosses to Clinton 59. Pair No. 2 consisted of the varieties Benton and Bentland that also differed mainly by the same genetic factor for resistance which had been introduced into Bentland by a cross of Benton × Landhafer, followed by six backcrosses to Benton.

There is little difference between the members of these pairs of varieties in appearance or in yield and quality of grain, when grown in the absence of crown rust, as was shown by 16 replicated field-plot trials conducted in Indiana from 1954 to 1956 by Newman *et al.* (*3*). Crown rust was absent in 15 of these trials and occurred as only a trace in one. The mean yields and bushel weights of the two pairs of varieties for this period, obtained under crown-rust-

Table 1. Comparative grain yields of crown rust susceptible (nontolerant), susceptible (tolerant), and resistant oat varieties. Reactions to crown rust: Clinton 59, susceptible, nontolerant; Clintland, resistant; Benton, susceptible, tolerant; Bentland, resistant.

Variety	Crown rust free (Av. yield 1954–56*)		Exposed to severe crown-rust attack					
			1955		1956		1957	
	bu/acre	Diff. (%)	bu/acre	Diff. (%)	bu/acre	Diff. (%)	bu/acre	Diff. (%)
			"Isogenic" pair No. 1					
Clinton 59	69.3		109.1		86.8		43.3	
		−3.9		−20.7		−28.6		−54.0
Clintland	72.1		137.5		121.6		94.2	
			"Isogenic" pair No. 2					
Benton	64.3		91.9		100.5		74.0	
		+1.4		+ 5.4		− 6.5		−13.8
Bentland	63.4		87.2		107.5		85.8	
L.S.D. (5%)	2.1		21.4		10.1		16.6	

* Average of 16 replicated tests.

Table 2. Comparative test weights of crown rust susceptible (nontolerant), susceptible (tolerant), and resistant oat varieties. Reactions to crown rust: Clinton 59, susceptible, nontolerant; Clintland, resistant; Benton, susceptible, tolerant; Bentland, resistant.

Variety	Crown rust free Av. 1954–56*		Exposed to severe crown-rust attack					
			1955		1956		1957	
	lb/bu	Diff. (%)	lb/bu	Diff. (%)	lb/bu	Diff. (%)	lb/bu	Diff. (%)
			"Isogenic" pair No. 1					
Clinton 59	33.4		32.6		28.9		18.9	
		−2.9		−13.5		−11.3		−30.5
Clintland	34.4		37.7		32.6		27.2	
			"Isogenic" pair No. 2					
Benton	34.7		34.5		31.8		21.8	
		0.0		− 2.5		− 2.8		−21.9
Bentland	34.7		35.4		32.7		27.9	

* Average of 16 replicated tests.

free conditions, are presented in Tables 1 and 2 for comparison with their performance under crown-rust epidemics.

The same two pairs of varieties were exposed by us to severe, artificially induced, crown-rust epidemics in nursery-row performance trials in 1955, 1956, and 1957. The trials consisted of randomized, quadruplicate plots of each variety. Each plot consisted of four rows, 7.5 feet long, spaced 1 foot apart from which the center two rows were harvested for yield and bushel weight determinations. Mixed populations of physiologic races of crown rust that were highly virulent to Clinton 59 and Benton but avirulent to Clintland and Bentland were used in creating the crown-rust epidemics. The crown-rust infection reached 100 percent (maximum possible intensity) on the susceptible Benton and Clinton 59 in all three years, ultimately destroying all foliage, but in 1957 reached maximum proportions at an earlier stage of host development. In contrast, only a trace of crown rust developed on the resistant Bentland and Clintland.

Data on performance under rust attack are reported in Tables 1 and 2. In 1955 and 1956 the losses in yield, and in quality as measured by bushel weight, of the susceptible but tolerant variety Benton were nil or small as deduced from comparison with its resistant counterpart, Bentland. In contrast, the losses to the susceptible and nontolerant Clinton 59 were severe as deduced from comparison with its resistant counterpart, Clintland. Under the extremely severe epidemic of 1957 the same type of comparisons showed a yield loss of only 13.8 percent for Benton versus a 54.0 percent loss for Clinton 59. Likewise, the bushel weight of Benton was reduced 21.9 percent while that of Clinton 59 was reduced 30.5 percent.

Another measure of the tolerance of Benton is gained by direct comparison of its yield and quality with that of Clinton 59 (Tables 1 and 2). Both varieties appear to be completely susceptible to crown rust. Clinton 59 was significantly the higher yielding of the two in the absence of crown rust; yet under severe epidemics Benton gave much the higher yields in two out of the three years it was tested.

Since the crown-rust attacks on Benton and Clinton 59 appear to be equally massive, it is apparent that damage to functions and structures affecting yield and grain quality was much more severe in the variety Clinton 59 than in Benton. The losses of grain in Benton attributable to crown rust were not significant at the 5-percent level, while losses to Clinton 59 were significant. This performance would indicate a true tolerance of a high order in the susceptible variety Benton.

The tolerance exhibited by Benton should not be confused with intermediate degrees of rust resistance which have been erroneously referred to as tolerance despite the fact that they involve a degree of hypersensitivity. Varieties of such intermediate resistance, like those having more complete resistance, are also subject to "loss" of resistance in the presence of new races. This has been shown by experience with several oat varieties including Mo. 0-205 and Newton when subjected to race 216 of crown rust.

Theoretically, tolerance should be more stable than hypersensitivity-induced resistance. Should a physiologic race of the pathogen arise to which a previously tolerant variety would be nontolerant, the outcome would be a greater injury to the host with no consequent increase in the relative rate of proliferation of the newly arisen race as compared with that of the established races toward which tolerance is exhibited. This would provide no screening mechanism whereby the new race might gain an advantage over the established races and thereby replace them. This situation would be in marked contrast to the known competitive advantage gained by a new virulent race that can successfully parasitize a variety that is hypersensitive (resistant) to the prevalent races.

The heritability of tolerance to either oat crown rust or wheat leaf rust has not been investigated. Such studies have been initiated, and the possibility of introducing true tolerance into varieties of superior type, quality and yielding ability will be explored (*4*).

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2 May 1958

A Climatic Record from Searles Lake, California

Abstract. Data concerning past climatic conditions in arid California have been presented. Palynological and geological evidence points to the existence of past cooler moister climates and to climatic fluctuations. These have been tentatively correlated with late Pleistocene events in glaciated North America. The existence of a rather extensive woodland community at times of more favorable moisture conditions seems to be indicated.

The presence of dry lake basins in arid regions is strong evidence of a former rainfall/evaporation ratio much higher than at present (*1*). The sedimentary column in such basins should record this sequence both by inorganic and organic evidence, notably by changes in the content of fossil pollen derived from adjacent vegetation.

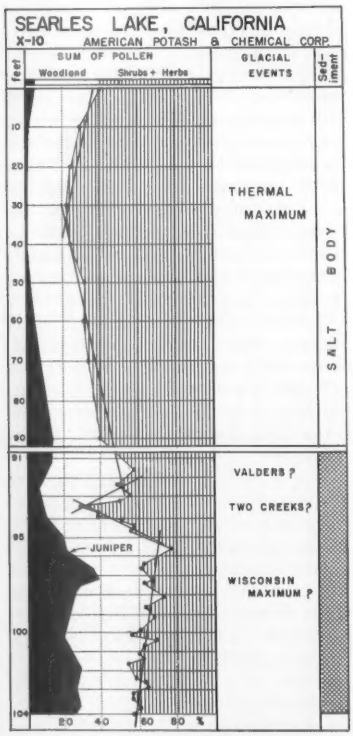

Fig. 1. Pollen diagram from Searles Lake, California. Depth in feet at left. Note change in scale at 90-foot level. All pollen percentages are measured from left (0 percent) of pollen diagram. Sediments generalized at right: 0 to 91.6 feet, salt body with thin layers of mud; 91.6 to 104.4 feet, parting mud. NAP maximum at 93 feet represents dry conditions during Two Creeks interstadial. Juniper maximum at 97 feet probably represents maximum precipitation/evaporation ratio for this basin, and should be correlative with the moisture peak of the Wisconsin maximum.

The most reasonable explanation of more humid conditions in the past is that they were associated with times of continental glaciation when precipitation was greater and temperature lower than is now the case. The analysis of sediment cores from such lakes is therefore of special interest to students of Pleistocene geology, climate, and vegetation.

The sediments in the basin of Searles Lake in the Mojave Desert of California are heavily saline as a result of intense and prolonged evaporation. Cores taken at site X-10 near the middle of the lake show an organic layer (parting mud) from about 104 to about 92 feet, while the upper 92 feet of deposit consists of saline material. This suggests that the organic layer is correlative with the most recent pluvial climate and that the salt above it is correlative with subsequent drier and warmer conditions (*2*).

Carbon-14 dating of the span of time represented by the organic deposit will, when available, confirm or discount this suggestion. Meanwhile the pollen analysis of the present core seems to exclude any other hypothesis (Fig. 1). Woodland species, save for one interesting fluctuation to be mentioned, are more numerous in the organic layer than above it, while the reverse is true of desert plants (shrubs and herbs).

Communities of woodland genera, essentially *Pinus* and *Juniperus*, do not, with one slight exception, now occur nearer the site than a distance of some 30 miles and an altitude of about 5000 feet. The core site is at altitude 1616 feet. The reasonable assumption is that vegetation zones have migrated up or down, away from or toward the basin, in response to appropriate climatic changes.

Details are reserved for later publication. Meanwhile attention is called to the woodland maximum just below 97 feet as indicative of a maximum precipitation/evaporation ratio. Further, a sharp decrease in this ratio is indicated above 94 feet, with a subsequent brief return to moister conditions. The position and character of this episode are exactly what should be expected if the episode were correlative with the Two Creeks interval of glacial retreat in the Great Lakes region, followed by an ice readvance. It further deserves notice that the Compositae, now represented by various shrubby species, reach a high level only in the upper saline deposit. A shift towards more intensified arid conditions above the 55-foot level is evidenced by a decrease in the percentage of *Artemisia* (sagebrush) and the dominance of chenopods (*3*, *4*).

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Saturation Curves of Orthorhombic Sulfur in the System $S\text{-}Na_2S\text{-}H_2O$ at 25° and 50°C

As a part of an investigation of the physicochemical processes involved in the origin of mercury ore deposits and associated sulfur deposits (*1*), we have determined at 25° and 50°C the saturation curves of orthorhombic sulfur in the concentration range from 100 percent H_2O to 80 percent H_2O. Previous work by Kuster and Heberlein (*2*) demonstrated that in Na_2S solutions there is a marked increase of solubility of sulfur with increasing concentration of Na_2S. Kuster and Heberlein, however, did not make a complete determination of the equilibrium relations since they did not determine the final equilibrium concentrations of Na_2S. They allowed sulfur to react with Na_2S solutions of known initial concentration until the solutions were saturated and then determined the equilibrium concentration of S in grams per cubic centimeter. Their data therefore do not make possible the determination of the exact position of the saturation curve in a triangular equilibrium diagram.

Baker reagent-grade powdered orthorhombic sulfur (99.95 percent) was used for all the solubility experiments. "Baker Analyzed" reagent-grade $Na_2S \cdot 9H_2O$ was rinsed with distilled water, and clear colorless material was set aside for use. Distilled water used to make up the experimental mixtures was boiled for at least 10 minutes to remove oxygen. The experimental samples were prepared by mixing orthorhombic sulfur, $Na_2S \cdot 9H_2O$, and boiled distilled water in Teflon (tetrafluorethane) bottles under an oxygen-free nitrogen atmosphere.

The Teflon bottles containing fine-grained orthorhombic sulfur and solutions of Na_2S were rotated in constant temperature baths at 25.00° (±0.02°)

and 50.00°C (±0.02°) for periods of 3 days to several weeks. The Na_2S and S contents of solutions allowed to react with orthorhombic sulfur for 3 days agreed with the Na_2S and S contents of solutions allowed to react for 3 weeks and longer, indicating that equilibrium was closely approximated. As a further check that equilibrium between the solid and liquid phases had been obtained, solutions initially supersaturated with sulfur were allowed to react for periods of 3 days to a week. The determined final concentration of sulfur in the solutions originally supersaturated with S agreed within ±0.01 percent with the sulfur concentrations of originally undersaturated solutions that were allowed to react for the same lengths of time. The microscope and x-ray diffractometer were used to identify the solid phase (orthorhombic sulfur) that was in equilibrium with the saturated solutions.

The saturated solutions were analyzed by a modification of a procedure of Dickson and Tunell (*3*) which involves the use of H_2O_2 to oxidize S^{--} ion to SO_4^{--} ion. In preparation for analysis the saturated solutions were filtered through a fritted glass filter to remove suspended solid sulfur and placed in a weight buret which was then allowed to come to room temperature. The filtered sample was divided into two portions, one to be analyzed for Na in the form of Na_2SO_4, and the other to be analyzed for total S in the form of $BaSO_4$. The samples were diluted with concentrated NH_4OH. Five percent H_2O_2 was added to oxidize the dissolved S and S^{--} ion to SO_4^{--} ion. The role of the NH_4OH was to prevent precipitation of sulfur when the H_2O_2 was added. One sample was analyzed for Na by weighing as Na_2SO_4, and the Na_2S concentration was calculated in weight percent. The other sample was analyzed for total S by weighing as $BaSO_4$. From the total S content was subtracted the calculated amount of sulfur contributed by Na_2S to obtain the saturation concentration of sulfur in weight percent. Water percentages were determined by difference. Table 1 presents the experimental data.

Portions of the saturation curves of orthorhombic sulfur in the system S-Na_2S-H_2O at 25° and 50°C are shown in Fig. 1. The compositions of analyzed saturated solutions are represented by points within circles for 25°C, and points within triangles for 50°C.

On the scale of Fig. 1 the data for the 25°C saturation curve appear to fall along a straight line. However, if the data are plotted on a larger scale, a slight convexity toward the unsaturated solution field is evident. The convexity indicates that the ratio of dissolved S to total Na_2S decreases with decreasing concentration of Na_2S. Therefore, diluting a saturated solution at 25°C tends to cause sulfur to precipitate, and evaporating a saturated solution at 25°C in contact with sulfur tends to cause more sulfur to dissolve. However, because the saturation curve is nearly a straight line, the amount of sulfur precipitated or dissolved as a consequence of dilution or evaporation is small.

Table 1. Solubility of sulfur in sodium sulfide solutions (percentage by weight).

Na_2S	S	H_2O (by difference)
At 25.00°C (±0.02°)		
0.86	1.33	97.81
1.38	2.11	96.51
1.97	3.03	95.00
1.98	3.05	94.97
3.19	4.98	91.83
3.51	5.45	91.04
4.17	6.45	89.38
7.42	11.48	81.10
At 50.00°C (±0.02°C)		
0.63	1.15	98.22
0.71	1.30	97.99
1.56	2.70	95.74
2.64	4.39	92.97
4.17	6.55	89.28
6.00	8.94	85.06
6.41	9.47	84.12

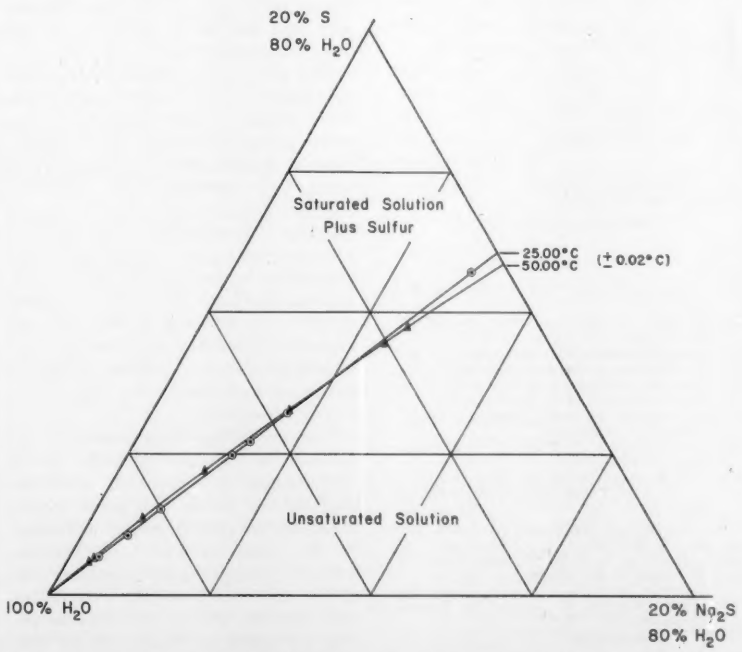

Fig. 1. Saturation curves of orthorhombic sulfur in the system S-Na_2S-H_2O at 25° and 50°C. The compositions of analyzed saturated solutions are represented by points within circles for 25°C, and by points within triangles for 50°C.

The 50°C saturation curve is concave toward the unsaturated solution field, indicating that the ratio of dissolved S to total Na_2S decreases with increasing concentration of Na_2S. The effect of diluting or evaporating a saturated solution at 50°C is opposite to that of diluting or evaporating a saturated solution at 25°C. Dilution of a saturated solution at 50°C in contact with sulfur will allow more sulfur to dissolve; on the other hand, evaporation tends to cause sulfur to precipitate. The stronger curvature of the 50°C isotherm indicates that the effect on the amount of sulfur dissolved or precipitated as a consequence of dilution or evaporation is greater than the effect of dilution or evaporation of saturated solutions at 25°C.

Figure 1 shows that the temperature coefficient of solubility varies with the Na_2S concentration. At concentrations of Na_2S below about 5 percent the solubility of sulfur increases with increasing temperature; above 5 percent Na_2S the solubility of sulfur decreases with increasing temperature. The maximum positive temperature coefficient of solubility is approximately 0.4 percent per degree centigrade at about 2 percent Na_2S.

The following reactions are probably involved in the heterogeneous and homogeneous equilibria:

$$S^{--} + H_2O \rightleftharpoons HS^- + OH^-$$

$$HS^- + H_2O \rightleftharpoons H_2S + OH^-$$

$$nS + S^{--} \rightleftharpoons S^{--(n+1)} \qquad (4)$$

$$4S + 6OH^- \rightarrow S_2O_3^{--} + 2S^{--} + 3H_2O$$

The reversal of the sign of the temperature coefficient of solubility and the

different shapes of the curves imply that the effects of various reactions which compete for sulfur shift with changing temperature and Na_2S concentration.

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28 April 1958

Occurrence of Serotonin in a Hallucinogenic Mushroom

Although some doubt has been cast recently upon the identification of *teonanacatl,* the sacred fungus of the Aztecs, as a species of *Panaeolus* (*1*), members of this genus are well known for their hallucinogenic properties and remain as the classical examples of mushrooms producing mycetismus cerebralis (*2*).

A preliminary chromatographic survey of a number of toxic mushrooms collected in western Washington (*3*) revealed the presence of several compounds in *Panaeolus campanulatus* (Fr.) Quélet (*4*) which gave, with Ehrlich's reagent, color reactions characteristic of indole derivatives. Subsequent investigation revealed that the most abundant of these compounds exhibited properties identical with those of serotonin (5-hydroxytryptamine). Although this compound has previously been detected in animals (*5*) and higher plants (*6*), this is the first report of its occurrence in a fungus. Its dimethyl derivative, bufotenin, has been reported to exist in certain species of *Amanita* (*7*).

It should not be assumed that serotonin, per se, is the hallucinogenic principle in *Panaeolus campanulatus* since Waalkes *et al.* (*6*) have established that large (20 mg) oral doses of the compound do not produce physiologic effects in human beings. The presence of serotonin may be indicative of the presence of related indole compounds, possibly of the type recently isolated from *Psilocybe mexicana* Heim (*8*). This compound, which has been named psilocybin, causes psychotropic effects in human beings following oral administration.

One gram of the dried mushroom was extracted with 70 percent ethanol, the extract was concentrated in a vacuum at 45°C, and the residue was purified by partition between *n*-butanol and water essentially as described by Udenfriend *et al.* (*5*). The purified extract was concentrated, and the entire quantity deposited as a line on a sheet of Whatman No. 3 filter paper which was subjected to ascending formation with a wash liquid composed of *n*-propanol and 1*N* ammonia (5:1). The section of the sheet corresponding to serotonin was eluted with water, concentrated, and again purified by partition between *n*-butanol and water.

The residue thus obtained was identical chromatographically with serotonin (*9*) in four solvent systems: the *n*-propanol–ammonia system described above, *n*-butanol–acetic acid–water (4:1:5), *n*-butanol saturated with 1*N* hydrochloric acid and methyl ethyl ketone–acetone–water (20:2:5). It gave reactions identical in all respects with serotonin with Ehrlich's reagent, Pauley's reagent, cinnamic aldehyde followed by hydrochloric acid, and with Jepson and Stevens' reagent, the latter being highly specific for certain tryptamines (*10*).

The ultraviolet absorption spectrum of an aqueous solution of the compound at *p*H 5.4 had a minimum at 250 mμ, a maximum at 275 mμ, and a shoulder with a point of inflection at 300 mμ. This is in good agreement with the absorption characteristics previously reported for serotonin (*11*). From these data it was concluded that the compound obtained from *Panaeolus campanulatus* was serotonin.

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5 May 1958

Passage of Bacteriophage Particles through Intact Skin of Mice

It has long been known that two highly infectious species of bacteria, *Pasteurella tularensis* (*1*) and *Brucella melitensis* (*2*), can set up systemic infections in experimental animals when suspensions of such organisms are placed in contact with the apparently normal skin of animals. Rickettsia producing Rocky Mountain spotted fever can infect guinea pigs through the unabraded skin (*3*). Since bacteriophage particles are within the size range of most animal viruses but do not undergo either specific adsorption or multiplication in sensitive host tissues and have the added advantage of being assayed by relatively easy and accurate techniques, they lend themselves admirably to studies on the physical interactions of viruses in animals. Recent results from this laboratory (*4*) present evidence that bacteriophage particles can pass rapidly through the gastrointestinal barrier and into the blood circulation of mice. In view of the afore-mentioned results, experiments were initiated to ascertain whether particles of the size of bacteriophage could pass through the intact skin of mice.

The phage strain utilized in this study was derived from *Bacillus megatherium* 899a (lysogenic) and is the clear plaque mutant, strain C, as described by Gratia (*5*). The sensitive indicator strain *Bacillus megatherium* KM growing on a medium containing 2 percent Bacto Peptone was used for the production of phage stock suspensions, and assays were made by the pour plate method. Two different anatomical sites of adult white Swiss mice, strain C.F.W., Carworth Farms, were chosen as experimental areas—namely, the tail and the abdomen. These areas were not manipulated by any means such as depilation, shaving, or clipping of hair. In fact, great care was taken to choose only mice which by gross observation manifested normal and continuous dermis in these areas. In order to minimize the obvious effect that microscopic abrasions would have on these experiments, mice utilized in the tail experiments were isolated for 2 days prior to the experiments.

The mice were anesthetized for the duration of each experiment by the intraperitoneal administration of Pentathal sodium. In the first set of experiments the tail of each mouse was exposed to the virus solution (approximately 1×10^{10} phage/ml) by immersing it in a test tube to a level approximately 1 inch from the body proper. The tail was allowed to stay in contact with the virus solution for 15 minutes. In the second set of experiments, which were concerned with passage of bacteriophage through

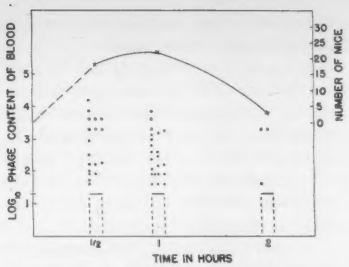

Fig. 1. Passage of *B. megatherium* bacteriophage through the skin of white mice. Numbers of active phage particles recovered from the total blood circulation of 96 mice. Thirty-two mice were tested at each time interval.

the skin of the abdomen, the same techniques were followed with the exception that the Pentathal sodium was administered by the subcutaneous route into the interscapular area of the mice instead of intraperitoneally. Two-tenths of a milliliter of the high-titer phage suspension was applied to the fur of the abdomen and gently spread with the tip of the pipette to effect penetration through the fur and onto the skin. The phage-treated area was equal in size to that of a 2.0 cm circle. At indicated time intervals after the administration of the bacteriophage suspension, the chest area was thoroughly sterilized with iodine and alcohol, and 0.1-ml samples of blood were taken by cardiac puncture with a heparinized 1-ml syringe. Following this procedure, the mice were sacrificed. Full-strength and serial two-fold dilutions of such blood samples were then assayed for the presence of virus particles. Control experiments on the accidental contamination of blood samples with phage were performed by placing 0.2 ml of the high-titer phage suspension on the chest area. After the routine sterilization procedure, blood samples were taken by cardiac puncture. From these as well as from other normal control animals no phage particles were recovered.

The recovery of active virus particles from the circulation of mice thus treated was quite irregular in both the number of positive recoveries and in the amount recoverable from the circulation of each mouse. There was essentially no difference in the rate and quantities of recovery by the two experimental methods. Figure 1 cites the cumulative results of one series of such combined experiments. The quantity of phage particles per 0.1 ml of sample has been converted by a factor of 20 and is cited for an average total blood volume of such mice of 2 ml. Thirty-two mice were sacrificed at each time interval. As can be seen, the number of mice yielding recoverable virus particles decreases with time, for only three mice yielded particles at 2 hours. These results suggest that this effect is possibly due to the immune mechanisms of the experimental animals. In this respect it is worth while to note that Van Vunakis *et al.* (*6*) have reported in vitro inactivation of *Escherichia coli* phage by normal mouse serum. The factor responsible was shown to be the properdin system previously described by Pillemer (*7*). Sulkin and his associates (*8*) reported evidence for the in vivo inactivation of *Staphylococcus* phage by the properdin system in rabbits.

In this study great variations in the recovery of active phage particles from the blood circulation were noted after intraperitoneal inoculations into different strains of normal mice. It may be possible that these variances were due to differences in titer of natural antibodies. Since current work is showing that the rate of arterial disappearance of this bacterial virus from the circulation of dogs is very rapid (*9*), the actual number of particles which were able to pass the skin barrier is possibly of a larger magnitude.

The size of the bacteriophage particles used in this study has been determined (*10*) to be 49 mμ for the width of the head and 330 by 15 mμ for the length and width of the tail. On the basis of the size of the head only, this particle then would be in the size range of the small animal viruses.

It is hoped that this report will stimulate reinvestigations of the possibility that virus infections may occur by penetrations through the intact skin and of the effects that this rather exotic mode of transmission may have in the epidemiology and pathogenicity of virus infections of man (*11*).

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Hemagglutinins in Uterine Secretions

Two kinds of findings have led to the suggestion that the ABO blood group phenotypes may be subject to the action of natural selection. One line of investigation has purported to show that there is a relative deficiency of living children of blood type A among the offspring derived from the "incompatible" mating, mother type O, father A (see, for example, *1, 2*). For a number of reasons considerable uncertainty exists concerning the existence and/or magnitude of this deficiency (*3*). The other line of investigation has suggested that in blood-group incompatible matings, the frequency of abortions is higher and the mean number of living children is lower than in compatible matings (*4*). (An incompatible mating is defined as one in which the male possesses an antigen which is lacking in the female; in the ABO system, the male possesses an antigen for which his spouse has the corresponding antibody.)

There are two possible mechanisms whereby selection due to the ABO blood groups may alter the number of children born with a given blood type. Many have assumed that immune antibodies produced by the mother could damage the fetus and result in its loss (for example, *1*). Another possibility, which formed the starting point for this investigation (*5*), is that selection may be exercised during the preconception period on the spermatozoa themselves. These two mechanisms are, of course, not mutually exclusive.

The postulate of spermatozoal selection involves one or more basic assumptions. One is that human sperm possess the specific blood group antigens of the donor. Previous findings on this point (for example, *6*) need to be reevaluated in light of the possible contamination of blood group substances in the seminal fluid. (Sperm from a nonsecreter donor would obviate such a possibility.) A second is that two antigenically different kinds of sperm are produced by a heterozygous AO male—that is, sperm bearing and sperm lacking A antigen. This antigenic dimorphism in the sperm population of heterozygous males has not, to our knowledge, been demonstrated. A third assumption, aside from the cellular antigens of the sperm, is that the presence of soluble blood group substances in the seminal fluid may itself be the (or one of the) determining agent(s) in spermatozoal selection.

If any of these assumptions is correct, then it becomes conceivable that there may be specific selection of sperm in the female reproductive tract, either by selective impedance of motility, complete inactivation, neutralization of a point of

attachment, or by some other, as yet unknown, mechanism. Such inactivation might also serve as a possible cause for infertility among otherwise physiologically normal couples.

The object of this study has been to determine whether or not the secretions of the uterine cervix contain hemagglutinins, as an initial step in an effort to work out the possible physiological basis for ABO selection. The impetus for the study stemmed from the feeling that the known facts regarding the consequences to the fetus of ABO isoimmunization (see 7) were not sufficient to account for the magnitude of selection effects postulated for ABO incompatible matings. The detection, some 30 years ago, of hemagglutinin in the cervical fluid was apparently limited to the analysis of a *single* sample (*8*).

All the women investigated in the course of this study were patients in the Out-Patient Gynecology Clinic of the University Hospital. Their reasons for the clinic visit were varied; only five were seen because of failure to conceive and in whom the cause of infertility was still unknown after careful study of the marital partners. The collection of cervical secretion depended only on whether or not a sample could be obtained from any particular woman. Blood for typing was obtained at the same time. All secretions were frozen soon after collection and all were tested within a period of 5 days.

The method of testing was as follows. To each tube containing the sample, which was usually quite small, was added 0.15 ml of saline. Because the quantity of secretion obtained varied from subject to subject, the dilution factor is variable. The contents of the tube were then thoroughly agitated with an applicator, the tube was centrifuged, and the clear supernatant fluid was tested with fresh A_1, B, and O red blood cells. All tests were performed in microtubes (6 by 50 mm) to which 0.01 ml of a 2 percent washed red blood cell suspension was added to 0.01 ml of the diluted secretion. The tests were allowed to stand for 1 hour at room temperature and were read macroscopically both before and after centrifugation.

The results are given in Table 1. Only distinctly positive reactions are tabulated, although the inclusion of weak, ambiguous reactions would not have substantially changed the magnitude of the difference presented in the table. Fifteen of the 35 diluted secretions (42.8 percent) of blood type O women contained antibody of the ABO system. Of 30 type A and 5 type B women, two cervical secretions (5.7 percent) had detectable antibody. Hemagglutinins were not found in the secretions of seven type AB women, which is additional evidence for the ABO group specificity of these antibodies. Only one of the women with cervical hemagglutinins had been seen because of infertility. A comparison of the findings in type O women with those in types A and B by the exact treatment of a 2×2 table yielded the two-tailed probability of 0.0053 that they were drawn from the same population. The fact that the over-all percentage of O, A, and B women exhibiting detectable hemagglutinins was only 24.3 may be due in part to the degree of dilution necessary to bring the volume up to 0.15 ml for scanty specimens, but this suggestion leaves unexplained the differences between A or B and O women. To some extent the latter differences may be due to the greater opportunity to detect agglutinins in O women, who have *two* agglutinins. Studies on undiluted secretions are in progress.

These findings would appear to support the possibility of gamete selection as a means of accounting for the distortions of the expected ratios in marriages of A fathers and O mothers, a possibility which, after the completion of this study, was discovered to have been proposed by Matsunaga in 1953 (*2*). Although several further lines of investigation readily present themselves, really critical data on this point may be difficult to obtain. The observed departures from the Mendelian ratios could be produced by a relatively slight impairment of sperm motility within women of the appropriate genotype, an impairment difficult to demonstrate with certainty. Inasmuch as the increased frequency of abortions in incompatible marriages seems securely established (*2, 9*), the present findings may indicate that the departure from Mendelian ratios in the children of A male × O female marriages has a complex background.

Note added in proof: It has recently come to our attention that the demonstration of antigenic dimorphism in the sperm of an AB male has been made by Gullbring (*10*). This finding would seem to support the possibility of preconception selection by blood group antibody in the uterine secretions.

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Table 1. Number of diluted uterine cervical secretions containing hemagglutinin, tabulated by blood type of the donors.

Blood type	No. tested	No. containing only anti-A	No. containing only anti-B	No. containing anti-A and anti-B	Total no. with hemagglutinins
A	30	0	2	0	2
B	5	0	0	0	0
AB	7	0	0	0	0
O	35	4	2	9	15
Totals	77	4	4	9	17

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24 April 1958

Concentration of Albumin in Renal Papilla

Recent investigations (*1*) have focused attention on the renal papilla for its role in concentrating urine. Freezing-point determinations of papillary tissue have demonstrated a tissue osmolarity up to three times that of the blood or renal cortex, because of a high concentration of sodium, chloride, and urea. Completely unsuspected, however, is the observation reported in this note of the high albumin concentration in the mammalian papilla. This may well bear an important relation to water transport in the papilla as part of the mechanism of concentrating urine.

Fourteen normally hydrated, nonanemic dogs were anesthetized with pentobarbital sodium. About 500 μc of I^{131}-labeled human serum albumin was injected systemically. The kidneys were exposed through an abdominal incision, and a loose tie was placed around the pedicle. In four dogs one kidney was ligated 3 minutes, the other kidney 60 minutes, after the injection of the radioactive material. In the remaining ten dogs both kidneys were ligated simultaneously after about 1 hour. The kidneys were removed and frozen in Dry Ice. Sections were cut on a band saw, and

pieces of the papilla were removed, placed in counting vials, and weighed. The tissue samples and 1 ml of arterial plasma obtained at the time of ligation were assayed for radioactivity in a well-type scintillation counter. The papillary concentration of labeled albumin was expressed relative to that of corresponding plasma from the following formula: Concentration of I^{131} albumin = (I^{131} counts per minute per gram of papilla)/(I^{131} counts per minute per milliliter of plasma).

The results are shown in Table 1. In about 1 hour the papillary I^{131} albumin concentration corresponded to that of 0.35 ml of plasma (±0.09 ml S.D.). In 3 minutes the corresponding value averaged about 85 percent of the 60-minute value of the same animals. Autoradiographs taken from kidneys ligated at 3 and 60 minutes were very similar and showed a considerably higher concentration of albumin in the renal papilla than in other anatomical regions of the kidney (Fig. 1).

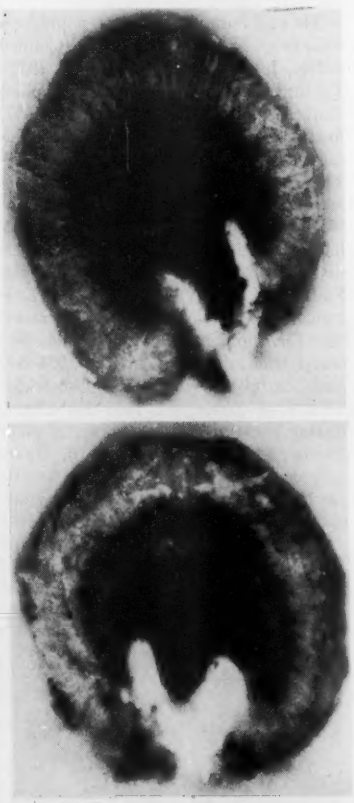

Fig. 1. (Top) Autoradiograph of a transverse slice of dog kidney obtained after the kidney was allowed to equilibrate for 3 minutes with intravenously injected I^{131} human serum albumin. Note the concentration of albumin in the papilla. (Bottom) Autoradiograph of a transverse slice of dog kidney obtained after the kidney was allowed to equilibrate for 60 minutes with intravenously injected I^{131} human serum albumin.

Urine samples collected from the bladder at the end of the experiment were hypertonic in all dogs and were found to be essentially free from radioactivity. The albumin used contained less than 2 percent of nonprotein bound radioactivity. Similar low values were found in filtered homogenates of papillary tissue. In four additional studies, labeled canine albumin was used instead of human albumin with the same result. The papillary concentrations of radioactivity were found to correspond to 0.33, 0.33, 0.52, and 0.34 ml of plasma in these four dogs. All were studied 60 mintes after injection of the radioactive material.

These data indicate a large and rapidly equilibrating pool of albumin in the renal papilla. Since complete equilibration may not have been reached in 1 hour, the values presented are minimal values for the papillary albumin concentration. Thus it is to be concluded that 1 g of the renal papilla in the dog contains at least as much albumin as is contained in about 0.35 ml of plasma. Since dog plasma contains about 3 g of albumin per 100 ml, this would correspond to an absolute albumin concentration of about 1 percent (wt./vol.). If the albumin in this pool is assumed to exist in the same concentration as that of the blood plasma, the data would indicate an albumin space of at least 35 percent of the volume of the papilla. This albumin pool is not paralleled by a large pool of erythrocytes. By direct observation the papilla is usually quite pale. Actual measurements of the red cell concentration of papillary tissue by means of Cr^{51}-labeled red cells have shown that the red cell content of the papilla is about 4 percent of its volume (*2*).

Preliminary studies in this laboratory have indicated that I^{131}-labeled human gamma globulin is incorporated more slowly than albumin into the renal papilla of dogs. This observation suggests that some portion of the papillary albumin is located extravascularly. In addition, the possibility of intravascular concentration of albumin above that of plasma must be considered. Since the papilla is exclusively perfused by postglomerular blood, a moderate concentration of intravascular papillary albumin to about one-third above that of plasma is to be expected. Histochemical observations of the renal papilla of rats have suggested that an intravascularly located plasma protein-bound esterase is concentrated several times above that of plasma (*3*). The very high values for the papillary albumin concentration found in this study are consistent with the hypothesis that the albumin in the papillary vessels is concentrated two or three times above that of plasma. If this hypothesis is correct, then water must have been removed from the plasma during its passage down into the papilla. This might be accomplished by means of the counter-current exchange of water in the vascular bundles of the renal medulla. An unusually high gradient of oncotic pressure may thus be maintained in the papilla, favoring the rapid net transport of water from the interstitial spaces into the papillary blood vessels (*4*).

Table 1. Albumin concentration in the renal papilla. In dogs 1, 2, 3, and 4 one kidney was removed 3 minutes after the injection of the radioactive albumin. The albumin concentrations in these papillae corresponded to 0.23, 0.18, 0.23 and 0.32 ml of plasma, respectively. This is about 85 percent of the corresponding 60-minute value of the same animals. For dogs 5 to 14 the values given in the table are the averages obtained from simultaneously ligated kidneys.

Dog	Time of ligation (min)	Albumin concn. relative to plasma
1	60	0.29
2	60	0.22
3	60	0.31
4	60	0.32
5	40	0.29
6	42	0.38
7	61	0.38
8	63	0.47
9	64	0.37
10	73	0.54
11	73	0.45
12	60	0.26
13	60	0.22
14	67	0.33
Av.		0.35
Standard deviation		± .09

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References and Notes

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4 April 1958

Association Affairs

Election of AAAS Officers

The AAAS Committee on Nominations has selected the following candidates for the offices of president-elect and members of the Board of Directors on the basis of a preliminary balloting of AAAS Council members:

President-elect (one to be elected)
Chauncey D. Leake
Thomas Park
William W. Rubey

Members of the Board of Directors (two to be elected)
Barry Commoner
H. Bentley Glass
Clyde K. Kluckhohn
Margaret Mead

The Board members whose terms expire at the end of 1958 are Chauncey D. Leake and Margaret Mead.

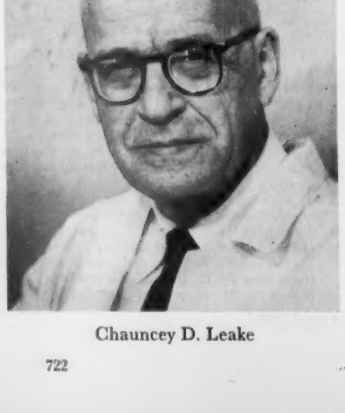
Council members will receive ballots for election by preferential mail vote by 10 November. Election procedures established by the Council provide that additional candidates for any of the elective offices may be nominated and included on the ballot by a petition signed by no fewer than 30 members of the Council and submitted to the executive officer no later than 1 November. The results of the election will be announced on 27 December at the Association's 1958 annual meeting in Washington, D.C. Biographical data concerning each of the candidates follow.

Chauncey D. Leake, 62 (pharmacology, physiology, history of science, health administration), Chemical Warfare Service, instructor in physiology, assistant professor of pharmacology, University of Wisconsin, 1919–28; professor of pharmacology and of history of medicine, lecturer in human relations, librarian, University of California Medical Center, San Francisco, 1928–42; council member, California Academy of Science, 1936–42; director, professor of pharmacology and of history and philosophy of medicine and public health, University of Texas Medical Branch, Galveston, 1942–55; professor of pharmacology, assistant dean, Ohio State University, 1955–; special award, International Anesthesia Research Society, 1928; president, History of Science Society, 1936–37; vice president, Society for Experimental Biology and Medicine, 1941–42; president, American Society for Pharmacology and Experimental Therapeutics, 1958; president, George Sarton Memorial Foundation, 1958; chairman, Section on Pharmacology, American Medical Association, 1934; president, Honorary Consultants Army Medical Library, 1946–47; consultant, U.S. Department of Defense, U.S. Public Health Service, Veterans Administration; chairman, National Research Council Committee on Problems of Alcohol, 1947–54; member, Committee on Cardiovascular Literature Project, 1957–58; founder and former editor of *University of California Publications in Pharmacology* and of *Texas Reports on Biology and Medicine*; editor, American Lectures in Pharmacology; associate editor, *Isis, Journal of the History of Medicine, Excerpta Medica, Archives internationales de pharmacodynamie et de thérapie,* and *Geriatrics*; member, board of trustees, *Biological Abstracts,* 1956–; visiting member, Institute for Advanced Study, 1950, 1952, 1956; Logan Clendenning lecturer, University of Kansas, 1951; Wm. Snow Miller lecturer, University of Wisconsin, 1940, 1957; Josiah Trent lecturer, Duke University, 1956; Poynter lecturer, University of Nebraska, 1957.

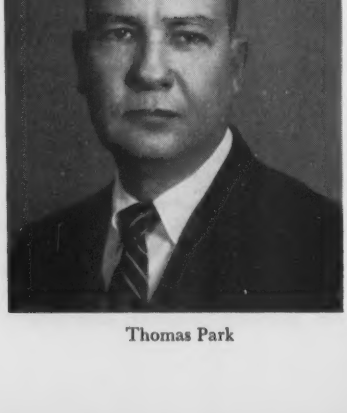
AAAS activities: vice president and chairman of Section L, 1942, 1954; delegate to the British Association for the Advancement of Science, 1953; member, Publications Committee, 1954–; member, Board of Directors, 1955–58; chairman, Committee on Social Aspects of Science, 1957–.

Thomas Park, 50 (zoology, population ecology), National Research Council fellow, Johns Hopkins University, 1933–35; instructor in biology, Johns Hopkins University, 1935–36, associate, 1936–37; instructor in zoology, University of Chicago, 1937–39, assistant professor, 1939–42, associate professor, 1942–47, professor, 1947–, associate dean, Division of Biological Sciences, 1943–46; Rockefeller Foundation fellow, Oxford University, 1948; scientific attaché, American Embassy, London, 1949; president, Ecological Society of America, 1959; member, Environmental Biology Panel, National Science Foundation, 1956–58; member, policy committee, American Society of Zoologists, 1957–58; editor, *Ecology,* 1940–50; editor, *Physiological Zoology,* 1955–; editorial board, *Quarterly Review of Biology,* 1938–; *American Naturalist,* 1951–59; zoological adviser, *Encyclopaedia Britannica,* 1950–.

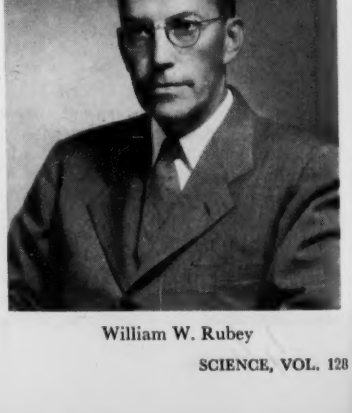
AAAS activities: member, Board of



Chauncey D. Leake



Thomas Park



William W. Rubey

Directors, 1954–; chairman, Publications Committee, 1955–; member, Newcomb Cleveland Prize Committee, 1956–58.

William W. Rubey, 59 (geology), instructor in geology, Yale University, 1922–24; successively geologic aid to principal geologist, 1920–44, geologist in charge, division of areal geology and basic sciences, 1944–47, research geologist since 1947, U.S. Geological Survey; chairman, division of geology and geography, 1943–46, general chairman, 1951–54, National Research Council; member, committee on geophysics and geography, Research and Development Board, 1947–50; president, Geological Society of America, 1949–50; vice president, American Geological Institute, 1950–51; member, divisional committee on mathematical, physical and engineering sciences, National Science Foundation, 1951–55; member, board of directors, Geochemical Society, 1955–57; councillor, American Philosophical Society, 1956–; visiting professor of geology, Institute of Geophysics, University of California (Los Angeles), 1954, California Institute of Technology, 1955, Johns Hopkins University, 1956.

AAAS activities: member, Board of Directors, 1957–; member, Committee on Section E, 1939–42; member, Newcomb Cleveland Prize Committee, 1951; representative on board of directors, Science Service, 1956–; member, Executive Committee, 1958.

Barry Commoner, 41 (cellular physiology and biochemistry), university fellow, Harvard, 1937–38, assistant in biology, 1938–40; instructor, Queens College (N.Y.), 1940–42; lieutenant, U.S. Naval Reserve, active duty, 1942–46; associate editor, *Science Illustrated*, 1946–47; associate professor of plant physiology, Washington University, 1947–53, and professor, 1953–, chairman, Committee on Molecular and Cellular Biology, 1957–, secretary, Committee on Cancer Research, 1953–; awarded AAAS Newcomb Cleveland Prize, 1953; naval liaison officer, U.S. Senate Committee on Military Affairs, Subcommittee on War Mobilization to assist in preparation of National Science Foundation Bill, 1946; member, honorary advisory panel, *Problems of Virology*, 1957–; member, editorial board, *International Review of Cytology*, 1957–; council member, Federation of American Scientists, 1957; chapter president, Society of the Sigma Xi, 1957–58; chapter president, American Association of University Professors, 1958.

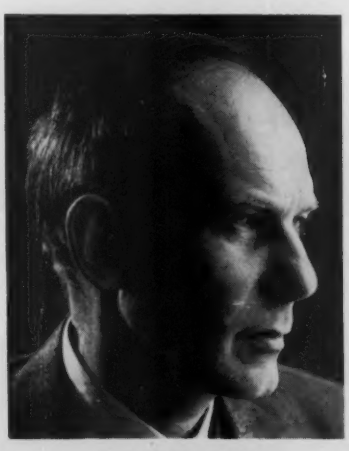
AAAS activities: secretary of Section G, 1954–; member, Committee on Social Aspects of Science, 1956–; chairman, Committee on AAAS Research Grants, 1954–; member, Committee on Popular Books in Science, 1956–; member, Steering Committee, AAAS Parliament of Science, 1958.

Barry Commoner

H. Bentley Glass

H. Bentley Glass, 52 (genetics), teaching fellow, Baylor University, 1928–29; National Research Council fellow, genetics, University of Oslo, Kaiser-Wilhelm Institute, and University of Missouri, 1932–34; instructor in zoology, Stephens College, 1934–38; assistant professor of biology, Goucher College, 1938–41, associate professor, 1941–45, professor, 1945–47; associate professor, Johns Hopkins University, 1947–52, professor, 1952–. Consultant, U.S. Department of State, Germany, 1950–51; member of the governing board, American Institute of Biological Sciences, 1951–53, president, 1954–56; assistant editor, *Quarterly Review of Biology*, 1944–48, associate editor, 1949–58, editor, 1958–; editor, *McCollum-Pratt Symposia*, 1949–; editor, *Survey of Biological Progress*, 1954–; biology editor, Houghton Mifflin Co., 1946–; member of the board of trustees, *Biological Abstracts*, 1956–, president, 1958–; secretary, American Society of Naturalists, 1950–52, member, executive committee, 1953; member of council, American Genetic Association, 1952–; member of council, American Association of University Professors, 1949–52, chairman, Special Committee on Academic Freedom and Tenure in the Quest for National Security, 1955–56, chairman of Committee A, 1956–58, president, 1958–60; secretary, American Society of Naturalists, 1950–52; chairman, Conference of Biological Editors, 1957–59; director, Survey of Biological Abstracting, 1952–54; member, Advisory Committee for Biology and Medicine, Atomic Energy Commission, 1955–61; member, National Academy of Sciences Committee on the Genetic Effects of Atomic Radiations, 1955–; member, executive committee of National Committee on Radiation Protection, 1957–; member, Baltimore Board of School Commissioners, 1954–58; member, National Science Foundation Genetics Panel, 1956–.

AAAS activities: vice president and chairman, Section F, 1956; member, Editorial Board, 1948–; acting editor,



Clyde K. Kluckhohn

Margaret Mead

Science and *The Scientific Monthly*, 1953.

Clyde K. Kluckhohn, 53 (anthropology) assistant professor of anthropology, University of New Mexico, and research associate, School of American Research, 1932–34; instructor in anthropology, Harvard, 1935–37, assistant professor, 1937–40, associate professor, 1940–46, professor, 1946–, director, Russian Research Center, 1947–54; Lowell lecturer, Boston, 1944; Guggenheim fellow, 1945–46; Dyason lecturer, Australian Institute of Internal Affairs, 1952; fellow, Center for Advanced Study in the Behavioral Sciences, 1954–55; staff member, School for Overseas Administration, 1943–44; co-chief, Joint Morale Survey, Military Intelligence Service and Office of War Information, 1944–45; expert consultant to the Secretary of War, 1946–47; consultant, Research and Development Board, Department of Defense, 1948–54; consultant, Office of Indian Affairs, Department of the Interior, 1942–; member, Advisory Committee, Foreign Service Institute, Department of State, 1956–; president, American Anthropological Association, 1947; chairman, Division of Anthropology and Psychology, National Research Council, 1956–; trustee, Institute for Inter-Cultural Studies; trustee, Harvard-Yenching Institute, 1949–54; member, Scientific Advisory Board, Fels Institute; director, Association on American Indian Affairs; awarded Viking Medal for General Anthropology, 1950.

AAAS activities: member, Executive Committee, Section H, 1940–43, vice president and chairman, 1950.

Margaret Mead, 56 (anthropology), National Research Council fellow, 1925–26; Social Science Research Council fellow, 1928–29; assistant curator of ethnology, American Museum of Natural History, 1926–42, and associate curator, 1942–; visiting lecturer, Vassar College, 1929–41; director, Wellesley School of Community Affairs, 1944; visiting lecturer, Columbia University, 1947–54, adjunct professor, 1954–, director of research in contemporary cultures, 1948–52; visiting professor, University of Cincinnati, 1957–58; executive secretary, National Research Council Committee on Food Habits, 1942–45; consultant on mental health and member of research committee, Mental Health Division, National Advisory Mental Health Council, U.S. Public Health Service; president, World Federation for Mental Health, 1956–57; president, Society of Applied Anthropology, 1949; member, editorial board, *American Scholar*; secretary, Institute for Intercultural Studies, 1949; chairman, Section of Anthropology, New York Academy of Sciences.

AAAS activities: member, Board of Directors, 1955–58; member, Committee on Social Aspects of Science, 1957–; chairman, Nominating Committee, 1957.

Letters

Use of Twins in Epidemiological Research

The work of Osborne and Adlersberg on serum lipids in adult twins [*Science* **127**, 1294 (1958)] seems to us to be important, both because of the findings and because of the epidemiological method employed. We have therefore reviewed critically the experimental design and the results obtained.

One factor which is hard to assess in this study is the extent to which the sample is biased as a result of the difficulty of obtaining pairs of twins. It is clearly too much to expect that the subjects used will be selected at random from the target populations; the best one can do is to take available subjects, recognize the major sources of bias, and draw conclusions that are subject to the serious limitations imposed by these biases. For example, since the level of serum lipids changes with age [D. Adlersberg, *J. Am. Med. Assoc.* **162**, 619 (1956)], one would be cautious in making comparisons between any groups that differed in the distribution of ages. As some of the groups in this investigation were small and the age of the subjects ranged from 18 to 55 years, it may well be that age differences influenced the results obtained. Further, one would expect that, as age increased, twins would be more likely to live apart. If this occurred, the effect of environmental differences due to living apart would be partially confounded with differences due to age.

The authors classified twins into five main groups according to sex and zygosity; monozygous male, monozygous female, dizygous male, dizygous female, and dizygous of unlike sex. The numbers belonging to these groups at birth are approximately in the ratio of 1:1:1:1:2 [F. Sandon, *J. Roy Statist. Soc.* **120A**, 440 (1957)]. It is not essential that the population proportions should be preserved in the sample, provided that the sampling is representative, in each case, of the appropriate group. However, when, as in this instance, the proportions are changed considerably (the dizygous male group and the dizygous group of unlike sex, in the sample, are relatively small) and random sampling has not been explicitly applied, one becomes suspicious that selective factors might be operating. The same kind of point could be made by noting that the monozygous pairs outnumber the dizygous by 43 to 39, that female pairs are more numerous than males in the ratio of 46 to 27, and that the number of female pairs living together is the same as the number living apart; in each case the deviation from the corresponding population ratios is considerable.

Each of the five groups of twins described above was subdivided according to whether the twins lived together or apart. It seems likely that twins living apart would be relatively hard to enlist as subjects, and that those living apart who came into the sample might therefore be unrepresentative of their appropriate groups. The authors note that they obtained only two pairs of dizygous male twins living apart. In our experience, twins living together are likely to appear at the laboratory together, and thus to have blood drawn at the same time of day, under similar circumstances, and to have it analyzed in the same batches. When this happens, important sources of intrapair variance are controlled, and the data are not strictly comparable with data obtained in the absence of such controls.

A point in the analysis of the data calls for comment. In computing an interpair variance for 14 pairs of monozygous male twins living in the same house and for 5 pairs living apart, the authors used a common mean for the 19 pair averages and thus obtained 18 degrees of freedom for a pooled interpair variance. This procedure is biased in the direction of increasing the interpair variance in those cases where there is a difference between the means of the "together" and "apart" groups. Indeed, the conventional method of detecting a difference between the means of twins living together and twins living apart would be to test for nonrandom enlargement of the interpair variance as calculated by the authors. This potential bias resulting from differences in the group means is avoided if interpair variances are computed separately for the two groups, and subsequently pooled (unless they are significantly different).

The authors are to be congratulated on their attempt to develop a new approach to an important epidemiological problem. Publication of their full data, including the ages of the subjects, may resolve some of the problems discussed above. It does seem, however, that there are special difficulties in studying, in this way, an age-dependent variable such as serum cholesterol. These difficulties are not so acute when the variable under consideration is something like blood group or intelligence quotient, which does not vary with age.

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JULIA B. ZALOKAR
MARTIN A. PILOT
Yale University School of Medicine, New Haven, Connecticut

We appreciate the interest of White, Zalokar, and Pilot in our paper ["Serum lipids in adult twins," *Science* **127**, 1294 (1958)] and the opportunity of adding

a few remarks which could not be presented in a brief report.

It is well established that serum cholesterol and serum phospholipid levels are sex- and age-dependent variables. From previous studies [Adlersberg *et al.*, *J. Am. Med. Assoc.* **162**, 619 (1956)], it is known that in males there occurs a significant increase of total cholesterol and phospholipids in serum from age 20 to age 33 years. In females, however, these levels do not change significantly from age 2 to 32 years, but a significant rate of increase occurs from age 33 to 58. Although the ages of the subjects ranged from 18 to 55 years in our sample, the majority fell into the third and early fourth decades. The age differences between the two groups compared were small, for example, in monozygotic male twins, those living together had a mean age of 25.04 and those living apart, of 28.20, a difference of only three years. The greatest age difference was encountered in female dizygotic twins; those living together had a mean age of 20.56 and those living apart, of 33.23. In these age periods, serum lipids are not an age-conditioned variable.

We sympathize with the difficulties apparently experienced by White and his coworkers in obtaining twins living apart for simultaneous study. Because of the extreme importance of this precaution, the simultaneous physical and chemical examination of the two members of a twin pair was made a *conditio sine qua non* in our study. Rigid application of this principle often required many months of negotiation with the twin subjects. In addition, all specimens obtained were labeled by number, and their identity remained unknown to the laboratory personnel. Thus, any extrinsic effects upon intrapair variances were reduced to the practicable minimum.

In any epidemiologic study of man, sampling poses one of the most difficult problems. In the sampling of adult twins in good general health, the incidence of sex and zygosity at birth is of limited value. Greulich concluded, as early as 1934, that the number of twins in the general adult population was approximately 50 percent of the incidence at birth [*Am. J. Phys. Anthropol.* **19**, 391 (1934)]. It is now well established that the sex and zygosity differential of twins in adulthood is subject during life to marked modifications. (The sampling of the twin population under study is discussed in detail in a monograph by Osborne and DeGeorge, now in preparation).

We fully agree with White *et al.* on the method of analysis to be used, and what they suggest had, in fact, been done. In our study the average lipid levels in the various groups were calculated, compared, and found not to differ significantly. Interpair variances were calculated separately and found not to differ significantly, and subsequently they were pooled.

The method of study, as well as the evaluation of the data, is discussed in greater detail in our paper entitled "Serum lipids, heredity, and environment: A study of adult twins [*Am. J. Med.*, in press].

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DAVID ADLERSBERG
Institute for the Study of Human Variation, Columbia University, New York, and *Departments of Medicine* and *Chemistry, Mount Sinai Hospital, New York*

Meetings

American Council on Education

The response of education in the United States to the sputniks and the challenges of the space age will be discussed by Arthur S. Flemming, Secretary of Health, Education, and Welfare, and other national leaders in education at the 41st annual meeting of the American Council on Education in Chicago, 9–10 October. The general theme, "Education Accepts New Challenges," will

be developed in the opening session at the Palmer House by Arthur S. Adams, president of the council, speaking on "A Clinical Look at the Controversy over Education," and by Virgil M. Hancher, president of the State University of Iowa, on "The New Challenges and How To Meet Them."

Other general session speakers include Nathan M. Pusey, president of Harvard University; Norman P. Auburn, president of the University of Akron; and Lawrence A. Kimpton, chancellor of the University of Chicago, who also is this year's chairman of the American council. The council's membership of 140 educational organizations and 1028 colleges and universities is expected to send nearly 1000 college presidents and other top administrators to hear the addresses and to participate in the discussion groups.

Pharmacology

At the fall meeting of the American Society for Pharmacology and Experimental Therapeutics, held at the University of Michigan, Ann Arbor, a resolution was introduced by Dr. Louis Goodman of the University of Utah, and President-Elect of the Society, commending the Past-President of the Society, Dr. Otto Krayer of Harvard, for his significant leadership of the Society in expanding its program of activity and in developing national headquarters in Beaumont House, Washington, D.C., in conjunction with the American Physiological Society. The resolution was adopted with acclaim. Chauncey D. Leake of Ohio State University presided, and Carl Schmidt of the University of Pennsylvania reported on medical education in Latin America. Bernard B. Brodie of the National Institutes of Health arranged a teaching institute on "Physicochemical Factors in Drug Disposition," and Leake held an informal discussion on teaching pharmacology to non-medical students. A total of 157 scientific reports were given in 16 sections, with emphasis on neuropharmacology and on cardiovascular and autonomic drugs.

Forthcoming Events

October

24–28. American Heart Assoc., San Francisco, Calif. (J. D. Brundage, 44 E. 23 St., New York 10.)

27–28. Child Research in Psychopharmacology, conf., Washington, D.C. (S. Fisher, Psychopharmacology Service Center, Natl. Inst. of Mental Health, Bethesda 14, Md.)

27–28. Plant Physiology, 9th annual research cong., Saskatoon, Saskatchewan, Canada. (D. T. Coupland, Plant Ecology

College of Agriculture, Univ. of Saskatchewan, Saskatoon.)

27–29. Radio, Institute of Radio Engineers, fall meeting, Rochester, N.Y. (V. M. Graham, EIA, 11 W. 42 St., N.Y.)

27–29. Weak Interactions, APS conf. (by invitation), Gatlinburg, Tenn. (J. L. Fowler, ORNL, P.O. Box X, Oak Ridge, Tenn.)

27–31. American Inst. of Electrical Engineers, fall general, Pittsburgh, Pa. (N. S. Hibshman, AIEE, 33 W. 39 St., New York 18.)

27–31. American Public Health Assoc., St. Louis, Mo. (B. F. Mattison, 1790 Broadway, New York 19.)

27–31. Metal Exposition and Congress, 40th natl., Cleveland, Ohio. (ASM, 7301 Euclid Ave., Cleveland 3.)

27–31. Vertebrate Speciation Conf., Univ. of Texas, Austin. (W. F. Blair, Dept. of Zoology, Univ. of Texas, Austin 12.)

27–1. Mental Health, 3rd Latin American cong., Lima, Peru. (B. Caravedo, Comite Peruano Organizador, III Congreso Latinoamericano pro Salud Mental, Avenida del Golf 1040, San Isidro, Lima.)

29–30. '58 Computer Applications symp., Chicago, Ill. (M. J. Jans, Armour Research Foundation, 10 W. 35 St., Chicago 16.)

30–31. Plastics, intern. symp., Philadelphia, Pa. (ASTM, 1916 Race St., Philadelphia 3.)

30–1. American Assoc. of Textile Chemists and Colorists, 37th natl. conv., Chicago, Ill. (J. G. Kelley, E. I. duPont de Nemours & Co., Inc., 7 South Dearborn St., Chicago 3.)

31–1. Central Soc. for Clinical Research, 31st annual, Chicago, Ill. (A. S. Weisberger, CSCR, Suite 1215, 25 East Washintgon St., Chicago.)

November

2–7. Radiology, 6th Pan American cong., Lima, Peru. (M. Lesonde, Inter-American College of Radiology, Tucuman 1516, Buenos Aires, Argentina.)

3–4. Italian Soc. of Nuclear Biology and Medicine, 3rd cong., Florence, Italy. (Segreteria della Societa Italiana di Biologia e Medicina Nucleare, Clinica Medica, Pisa, Italy.)

4. Use of 650 and 704 Computers for Structure Analysis, conf., Pittsburgh, Pa. (G. A. Jeffrey, Dept. of Chemistry and Physics, Univ. of Pittsburgh, Pittsburgh.)

4–7. American Soc. of Tropical Medicine, Miami Beach, Fla. (R. B. Hill, 3575 St. Gaudens Rd., Miami 33.)

4–11. International North Pacific Fisheries Commission, 5th annual (by invitation), Tokyo, Japan. (R. I. Jackson, 209, Wesbrook Building, Univ. of British Columbia, Vancouver 8, Canada.)

5–7. Society of Rheology, annual, Philadelphia, Pa. (W. R. Willets, Titaniaum Pigment Corp., 99 Hudson St., New York 13.)

6–7. Nuclear Science, 5th annual, San Mateo, Calif. (H. Pratt, IRE, 1 E. 79 St., New York 21.)

6–8. Geochemical Soc., St. Louis, Mo. (K. B. Krauskopf, Geology Dept., Stanford, Calif.)

(See issue of 19 September for comprehensive list)

Equipment

The information reported here is obtained from manufacturers and from other sources considered to be reliable. Science *does not assume responsibility for the accuracy of the information. A coupon for use in making inquiries concerning the items listed appears on page 738.*

■ TESTING MACHINE of 100-lb capacity is accurate within ± 0.5 percent of indication. Tensile, compression, transverse, or shear tests can be performed. Load measurement is provided by a calibrated pendulum. Draw-bar speeds up to 20 in./min are selectable. Standard grip clearance is 14¾ in. Output is a recorded curve. (W. C. Dillon & Co., Inc., Dept. 354)

■ RING LIGHT SOURCE is designed to produce "cold light" shadowless illumination of small objects for low-power microscopic inspection. The light is 2.5 in. in diameter with a 1¼-in. aperture through which the specimen may be observed. (Aristo Grid Lamp Products Inc., Dept. 356)

■ SOIL CONSOLIDATION TESTER applies a maximum pressure of 20 kg/cm² on a specimen 2.5 in. in diameter. Accuracy of the counterbalanced lever system used to adjust the load is ± 0.5 percent. The apparatus is portable. (Soiltest Inc., Dept. 358)

■ PULSE-HEIGHT ANALYZER consists of a 100-channel analog-to-digital converter and 20 channels of glow-transfer-tube storage. Any 20-channel group may be selected for data storage by means of a single switch setting. Linearity is 0.5 percent, and dead time is 500 μsec. The instrument contains all components necessary for a complete scintillation spectrometer except a phototube and crystal. (Tullamore Electronics Lab., Dept. 359)

■ GLOW-DISCHARGE UNIT for cleaning surfaces preparatory to vacuum coating is capable of delivering 400 ma at 5000 v d-c. This output is large enough to permit use in a 48-in. coater. Current is limited by a transformer that delivers approximately 90 percent of input power at full load. (Consolidated Electrodynamics Corp., Dept. 360)

■ PRINTER accepts parallel or serial input and prints from six to nine columns of digits in one or two copies. Output rate from parallel input is three lines per second; from serial input, four digits per second. An optional feature provides that the line to be printed is visible before and after printing. Paper slippage is less than 1/16 in. in 20 consecutive horizontal lines. The first copy can be torn off at any time. (Taller and Cooper Inc., Dept. 361)

■ RECORDING POTENTIOMETER can be adapted to handling from 2 to 24 channels by means of plug-in adapter units. Change to a different work load requires changing a plug-in unit, a dial indicator, and a print wheel. According to the manufacturer, this change can be completed in 3 min. Adaptation to various transducers and change of range can also be simply accomplished. Accuracy is 0.25 percent. (Weston Instruments Division, Daystrom Inc., Dept. 364)

■ FLUTTERMETER permits fine adjustment of recorder drives. To measure flutter, a prerecorded nominally 1000-cy/sec signal is played through the recorder. The fluttermeter amplifies frequency modulation of the signal by the recorder and indicates percentage of variation on its output meter in two ranges: 0 to 1.5 and 0 to 3.0 percent. Sensitivity is better than 30 mv. (Kay Electric Co., Dept. 365)

■ ACID PUMP of polyethylene attaches to 5-pt reagent bottle. Acid is delivered at 1000 ml/min by light, rapid squeezes of a plastic bottle that is part of the pump. Pressure on a relief valve stops flow without drip. (Fisher Scientific Co., Dept. 366)

■ PERFORATED TAPE READER is transistorized. The device will read five-, six-, seven-, or eight-level tapes at rates up to 1000 characters per second. Starting time is 3 msec, stopping time 0.2 msec. Tapes are read by photodiodes. (Potter Instrument Co., Inc., Dept. 362)

■ MELTING-POINT APPARATUS provides for simultaneous viewing of five capillary samples in a well-lighted, unobstructed field. A standard beaker is used as a container for the silicone-fluid heating bath. Electric heating is controlled by an autotransformer. A compressed-air fitting permits connection to an air line for rapid cooling. Capillaries are vibrated to insure uniform packing of the sample, and an adjustable stirrer provides uniform bath temperature. (Arthur H. Thomas Co., Dept. 383)

■ VACUUM LEAD-THROUGH TERMINAL is comprised of a high-alumina ceramic insulator fused to a metal lead-through pin. The terminal is designed to be used with soft solders or with hard solders at temperatures up to 1400°F. Various pin configurations are available. (Thermo Materials, Dept. 371)

■ RECORDER plots "on" time against total time on a 6- by 14-in. chart mounted on a drum. An accessory base provides digital display of the same information. (Gorrell & Gorrell, Dept. 375)

JOSHUA STERN
National Bureau of Standards

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Physiologist; B.Sc., chemistry; M.A., physiology, biochemistry; Ph.D. (1958 expected), physiology, biochemistry, pathology; 8 years' teaching and research. Medical Bureau, Burneice Larson, Director, 900 North Michigan, Chicago. X

POSITIONS OPEN

Biologist. Completed graduate work leading to Ph.D.; $5880–$7344; to study ecology and pollution of estuaries of Virginia. Virginia Fisheries Laboratory, Gloucester Point, Virginia. 9/19, 26; 10/3, 10, 17, 24, 31

Botanical and Cosmetic Chemist. An experienced botanical chemist and cosmetic chemist are required for an interesting and challenging overseas assignment. Liberal salary and benefits offered. Please send complete résumé to Box 212, SCIENCE. 10/3

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Technical Employment Coordinator
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(a) **Entomologist** to assist in conducting extensive trypanosomiasis research and control project to be carried out in Africa; 2-year tour of duty. (b) **Research Chemist,** Ph.D. for important supervisory position, research department, major company serving hospital and scientific fields; established 1894; new plant on 55-acre site; excellently equipped laboratories; college town, East. (c) **Scientist** with pharmaceutical or allied academic training and several years' industrial experience in pharmaceutical research development; Ph.D. helpful but not required; should be qualified to project coordination, large group of technical people; university city, East; $8000–$12,000. S9-4 Medical Bureau, Burneice Larson, Director, 900 North Michigan, Chicago. X

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Postdoctoral Traineeships in enzyme chemistry are available for 1959–60 at the University of Wisconsin, Institute for Enzyme Research in Madison. This program is supported in part by a training grant from the Division of Research Grants, U.S. Public Health Service, and the stipends provided correspond in amount to Public Health Service postdoctoral traineeship stipends. Application forms and information may be obtained by interested persons by writing to Dr. David E. Green, Program Director. 12/5

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Editor: James H. Shaw

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26 September 1958

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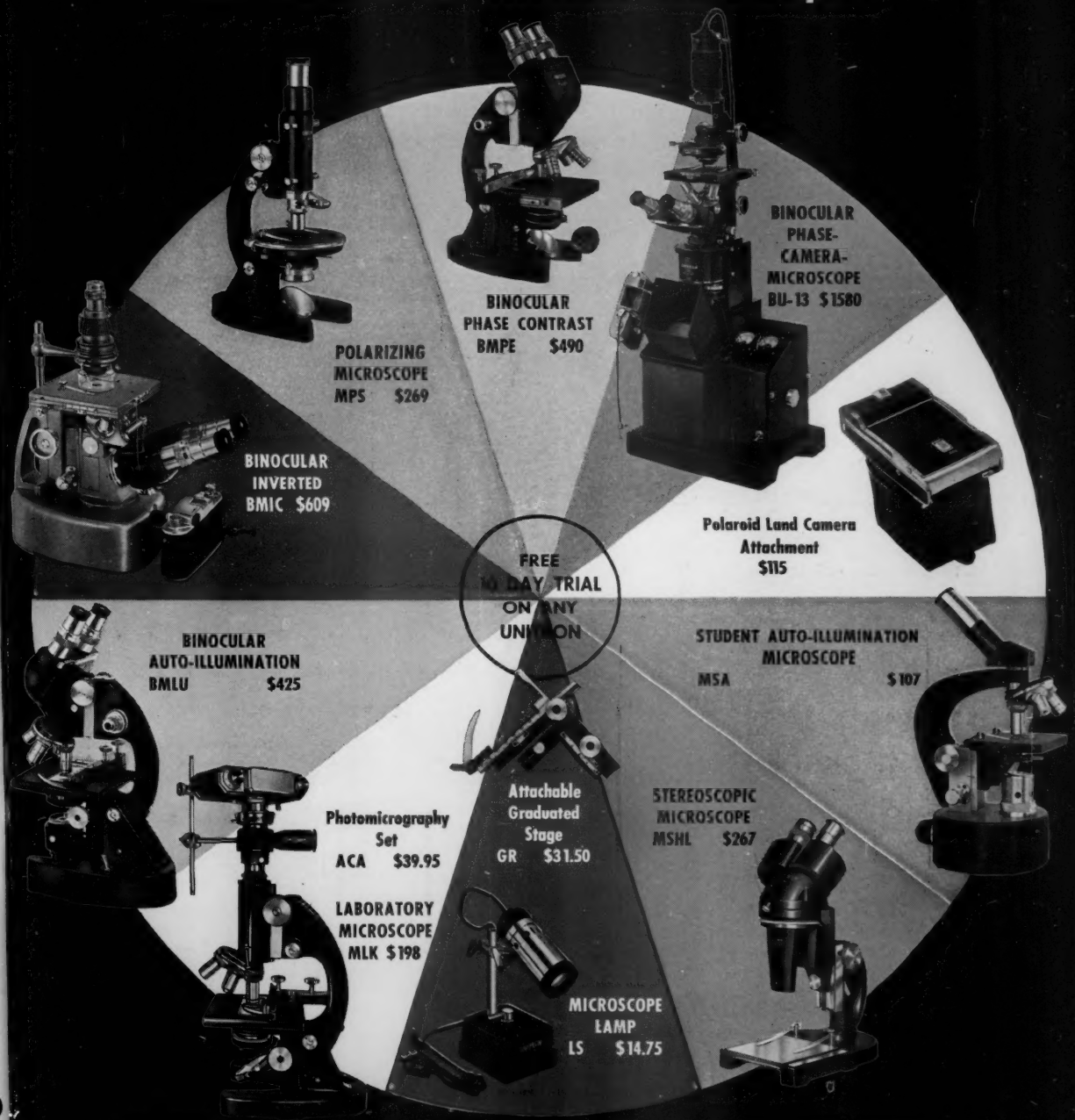

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